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# Can Wnt targeting finally take off? A systematic review on cancer prevalence after exposure to Wnt activating drugs

Journal:	BMJ Open		
Manuscript ID	bmjopen-2024-084934		
Article Type: Original research			
Date Submitted by the Author:	01-Feb-2024		
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Keywords:	ONCOLOGY, Adult oncology < ONCOLOGY, Breast tumours < ONCOLOGY		





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### Can Wnt targeting finally take off? A systematic review on cancer prevalence after exposure to Wnt activating drugs

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#### Abstract

Word count: 250/250

**Importance:** The association between Wnt pathway activation and cancer prevalence has not been described.

**Objective:** Assessing whether the use of drugs that activate the Wnt pathway leads to an increased cancer risk.

**Data sources and study selection:** PubMed, EMBASE and Cochrane databases were searched. All articles until November 17<sup>th</sup> 2023 were included. All primary research articles reporting clinical (observational and experimental) studies were included. Studies were eligible for inclusion if they included the exposure of interest (compounds that activate the Wnt pathway), and the outcome of interest (cancer prevalence).

**Data extraction and synthesis:** This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The search string, objectives, and study protocol methods were defined before the study was initiated. A total of studies 147 were included for full-text assessment.

**Patient(s):** Patients exposed to drugs that have been described to activate the Wnt pathway.

**Main outcome measure(s):** Main outcome was cancer and measures were prevalence, incidence, and risk estimate for cancer

**Result(s):** 43 studies investigating drugs that activate the Wnt pathway (valproic acid, lithium, cimetidine, olanzapine, clozapine, haloperidol) were included. Overall, there was no significant increase in the cancer risk among patients exposed to drugs that have been described to activate the Wnt pathway.

**Conclusions and relevance:** The use of drugs that activate the Wnt pathway is not associated with an increased cancer risk. As a promising agent in the regenerative therapy field, further research into Wnt activation as a treatment option should be explored.

Keywords: Wnt activating drugs; cancer prevalence; lithium; valproic acid.

Registration: Prospero ID: 286193

# Strengths and limitations of this study

- 25969 studies screened until November 17th, 2023
- Studies were eligible for inclusion if they included the exposure of interest (compounds that activate the Wnt pathway), and the outcome of interest (cancer prevalence)
- Aim to evaluate the association between activation of Wnt pathway and cancer prevalence
- Bbias was minimized by using two independent authors in the screening process.

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List of abbreviations

HR, hazard ratio

OR, odds ratio

RR, risk ratio

VPA, valproic acid

GSK 3, glycogen synthase kinase 3

MDS, myelodysplastic syndrome

SLE, systematic lupus erythematosus

Wnt, Wnt/Beta-catenin signaling pathway

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#### Introduction

The Wnt/ $\beta$ -catenin pathway is a signaling cascade that controls cell proliferation, cell polarity, and cell fate determination during embryonic development and tissue homeostasis (Nusse and Clevers 2017). Wnt/ $\beta$ -catenin signaling is known to be involved in development of multiple tissues, including brain, eye, ear, spinal cord, bone cartilage among many others (Steinhart and Angers 2018). In adulthood crucial roles in the function of intestine, bone and skin have been described for Wnt/ $\beta$ -catenin signaling (Steinhart and Angers 2018). Wnts (the ligands that activate the Wnt/ $\beta$ -catenin signaling pathway) are growth stimulatory factors that ultimately lead to cell proliferation (Niehrs and Acebron, 2012). Importantly, dysregulated Wnt signaling has been associated with several diseases such as degenerative diseases (Nusse and Clevers, 2017), neurodegenerative disorders (Kahn 2014; Berwick and Harvey 2012; Inestrosa, Montecinos-Oliva, and Fuenzalida 2012) schizophrenia (Inestrosa, Montecinos-Oliva, and Fuenzalida 2012) schizophrenia (Inestrosa, Montecinos-Oliva, and Fuenzalida 2012), aging-related tissue fibrosis (Hu et al. 2020), autoimmune diseases (Shi et al. 2016) and many types of cancer (Klaus and Birchmeier, 2008; Kumar et al., 2014; Lammi et al., 2004; MacDonald et al., 2009; Zhou et al., 2016).

Currently, targeting the Wnt/ $\beta$ -catenin signalling pathway, either by activating or inhibiting it, is being researched as therapy for some types of cancer (Gray et al. 2015; Rizzieri et al. 2016), neurodegenerative diseases (Leclair-Visonneau et al. 2016; Del Ser et al. 2013; Georgievska et al. 2013; Tolosa et al. 2014), hair loss (Jo et al. 2014; Tosti et al. 2016) and sensorineural hearing loss (McLean et al. 2021; Samarajeewa, Jacques, and Dabdoub 2019). When therapeutic agents target crucial developmental signaling pathways (such as Wnt, Notch, Hedgehog and bone morphogenic protein (BMP) pathways) serious and devastating effects on embryogenesis and carcinogenesis might arise due to increased cell proliferation. In line, continued activation of the Wnt pathway has been associated with therapy resistance in cancer patients and has been shown to promote self-renewal of cancer cells (Bugter, Fenderico, and Maurice 2021). Unfortunately, the effect of Wnt activation on cancer prevalence has not been consistently studied. In the last 15 years, common drugs used in the clinic have been described to activate the Wnt pathway (Riva et al. 2018; Taha et al. 2008). The most common Wnt activators used in the clinic are lithium and valproic acid (VPA), which have been used as treatment for psychiatric disorders since the 1960's (Ochoa 2022; Hedgepeth et al. 1997; Nagu et al. 2022). Besides, many novel therapeutic drugs have been synthesized specifically to activate Wht in the last 10 years and are used in the clinic (Augello et al. 2020). Many of these drugs activate the Wnt signaling pathway through the inhibition of glycogen synthase kinase 3 (GSK3) (Duda et al. 2020). This is one the most well studied mechanisms for activating the Wnt signaling pathway (Duda et al. 2020).

There are many novel therapeutic drugs in development for clinical usage that activate the Wnt pathway. However, safety concerns regarding its activation remain (P. Huang et al. 2019). Therefore we conducted a systematic review to address the

association between the use of drugs that activate the Wnt pathway and prevalence of any type of malignancy in the clinic. Our aim was to assess whether treatment with drugs that activate Wnt leads to an increased risk of cancer.

#### Methods

We evaluated all data available on clinical use of Wnt activators following the Prisma 2020 writing guideline for systematic reviews (Page et al. 2021). PICO framework was used to improve the search strategy (Schardt et al. 2007). The outcome of interest was the prevalence of any cancer, malignancy, or neoplasm, regardless of age, sex, and geographic location. The exposure of interest was any compound activating the Wnt pathway, regardless of indication, dosage and duration. An overview of the included compounds and their mechanism of action is available in **Table 1**.

#### Search strategy

The final search was done on November 17<sup>th</sup>, 2023. PubMed, Embase and Cochrane databases were searched. All articles until March November 17th were included in the search. On Embase, conference abstracts and reviews were removed. No further search filters were used. The search syntax consisted of names of medication with known Wnt activating properties used in the clinic combined with synonyms for 'cancer'. The full search strategy can be found in **Supplementary Table S1**.

#### Article selection

All primary research articles reporting clinical studies, including observational and experimental studies were included in this review. Studies were eligible for inclusion if they included the exposure of interest, i.e. compounds which have been described to activate the Wnt pathway, and the outcome of interest, i.e. cancer prevalence. Patients of all ages were eligible for this study. No control group was required. Articles assessing compounds with no clear Wnt activating properties were excluded. Animal studies, *in vitro* studies and non-primary research articles like review articles and letters were excluded. Three independent reviewers (A.A., S.B., N.S-C.) screened title and abstracts of collected studies after duplicate removal for eligibility criteria, and subsequently met and resolved disagreements. Full text screening was performed by two independent reviewers and disagreements were solved as above. Rayyan systematic review tool (Ouzzani et al. 2016) was used to semi-automate the primary screening.

#### Data extraction

A data extraction table was used to extract study characteristics and findings by two reviewers (A.A., N.S-C). with the software Microsoft Excel. The data extraction table included the following information: Study, indication for intervention, population, age, geographical location, used Wnt activator, used control group, cancer prevalence and cancer type (**Tables 2-10**). Authors were contacted if data was not reported in the article or otherwise unavailable. Data extraction was done by one author and checked by another author.

# Critical appraisal

The methodological quality of included articles was assessed using the Newcastle Ottowa-Scale (NOS) for nonrandomized studies as a reference guide (GA Wells et al. n.d.). Risk of bias in cohort studies was assessed for the following domains: selection bias, comparability of cohorts, and outcome (**Table 11 - 17**).

# Effect measures

Results were expressed according to the reported ratios from the published studies. This includes percentages, odds ratios (OR), risk ratio's (RR) and hazard ratio's (HR), in accordance with study design and available data. When unavailable, RR's and OR's were calculated. All ratios were used to answer the main questions qualitatively. No quantitative analyses were conducted for this systematic review.

# Results

# Article selection

Our PubMed database search until November 2023 yielded a total of 25969 articles. After duplicate removal, 19479 articles remained, that were screened for title and abstract. Following title and abstract screening, 147 articles were eligible for full text screening. After full text screening, 44 studies were included for this review. Main reasons for exclusion were outcome that was not in our inclusion criteria, publication type, study design, population, and different drug. Article screening is summarized in the flowchart in **Figure 1.** 

# Study characteristics

Included studies, which are summarized in **Tables 2-10**, consisted of 20 cohort, 17 casecontrol and 7 pharmacovigilance studies. Drugs with reported Wnt activating properties included were VPA (12 studies), lithium (13 studies), haloperidol (7 studies), cimetidine (10 studies), clozapine (7 studies), and olanzapine (7 studies). Some studies assessed multiple drugs of interest.

Studies were performed in multiple countries, including multiple European and Asian countries in addition to the USA. Additionally, a WHO pharmacovigilance database consisting of 160 countries was included (Chrétien et al. 2021). Most common indications were psychotropic, gastro-intestinal and neurologic use. All compounds were administered systemically in clinical dosing. Most studies assessed any type of cancer prevalence. All studies assessed cancer risk by analyzing clinical data or performing questionnaires. In addition, a few studies included histological verification for cancer diagnosis in addition to clinical data (Kaae et al. 2010; Cohen et al. 1998a; Pottegård et al. 2018; Kristensen et al. 2020). All Wnt activating compounds were used in their clinical dose respective to their indication.

#### Risk of Bias

Based on the Newcastle Ottawa Scale, all but one included study concerning VPA were determined to have good quality (**Tables 11&12**). One study by Stritzelberger et al. (Table 12) did not show all data concerning VPA (Stritzelberger et al. 2021).

For lithium 8 cohort studies and 5 case-control studies were included. For both cohort and case-control studies, most studies were determined to have low risk of bias (**Tables 13&14**). One cohort study by Zaidan et al. (**Table 13**) and two case-control studies by Kahan et al. and Tamim et al. (**Table 14**) were subject to a high risk of bias (Kahan et al. 2018; Tamim et al. 2008; Zaidan et al. 2014).

Most studies reporting cimetidine use had a high risk of bias (**Tables 15&16**). Main points were missing data, lack of control group or no comparability of groups. The cohort study by Velicer et al. (**Table 15**) was determined to be of fair risk of bias (Velicer, Dublin, and White 2006). Only the study by Rossing et al. (**Table 15**) was determined to be of low risk of bias (Rossing et al. n.d.).

For haloperidol, both the cohort study by Wang et al. (**Table 17**) and the case-control study by Friedman et al. (**Table 18**) were determined to have low risk of bias (Wang et al. 2002, Friedman et al. 2020). The risk of bias in the case-control study by Hsieh et al. (**Table 18**), was high because they used non-gastric cancers as a control for gastric cancer instead of healthy individuals with no cancer (Hsieh et al. 2019). The case-control study by Pottengard et al. (**Table 18**) was determined to be of good quality (Pottegård et al. 2018).

Outcomes

# VPA

7 cohort studies assessed the association between VPA use and cancer prevalence (Chavez et al. 2020; Yang et al. 2022; Singh et al. 2012; R.-Y. Huang et al. 2016; Kaae et al. 2010; Lin, Hsieh, and Wu 2018; Kang et al. 2014). 5 studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively (Yang et al. (2022), RR = 0.877 (0.642-1.032); Singh et al (2011), RR=1.18 (0.96–1.46), Huang et al. (2016), RR= 0.848 (0.563-1.277); Kang et al., 2014, RR= 0.848 (0.563-1.277); Kaae et al. (2010), HR = 0.96 (0.84-1.19) 1.0 (0.8-1.3) 1.0 (0.7-1.3)). The study by Chavez et al. evaluated melanoma prevalence in VPA exposed individuals. In this study, VPA exposed individuals had a significantly reduced prevalence of melanoma compared to controls (Chavez et al. (2020), HR = 0.64 (0.51-0.79)).

Additionally, 5 case-control studies assessed the association between VPA use and cancer prevalence (Hallas et al. 2009; Stritzelberger et al. 2021; Salminen et al. 2016; Kristensen et al. 2020; G. George et al. 2023). All studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively (George et al. (2023), OR= 0.85, 0.70-1.04; Hallas et al. (2009), OR= 1.21

(0.95-1.56); Stritzelberger et al. (2021) p =0,760; Salminen et al. (2016), OR= 0.62 (0.42-0.92); Kristensen et al (2020), no data on VPA available).

#### Lithium

8 cohort studies assessed the association between lithium use and cancer prevalence, including melanoma, urinary tract tumors, malignant neoplasms, invasive breast cancer and any type of cancer (Asgari et al. 2017; Kessing et al. 2015; Martinsson et al. 2016; R.-Y. Huang et al. 2016; A. George et al. 2020; Lin, Hsieh, and Wu 2018; Zaidan et al. 2014; Cohen et al. 1998). 5 studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively (Cohen et al. (1998), OR=1.19 (0.71-2.01); Kessing et al. (2015), RR= 1.01 (0.97-1.05); Martinsson et al. (2016), RR=1.04 (0.89-1.23); George et al. (2019), RR= 0.92 (0.58-1.46); Chia lin et al. (2018), RR=1 (0.6-1.6). Asgari et al. and Huang et al. evaluated cancer risk in lithium exposed individuals compared to controls. In both studies lithium exposed individuals had a significantly reduced cancer risk compared to controls (Asgari et al. (2017), unadjusted HR=0.68 (0.51-0.90); Huang et al. (2016), RR= 0.426 (0.186-0.975)). Zaidan et al., found an increased risk of renal tumors in patients exposed to over 20 years of lithium in comparison to both the general population and to kidney function matched controls (based on glomerular filtration rate) (Zaidan et al. 2014, p=0.04).

Additionally, 5 case-control studies assessed the association between lithium use and cancer prevalence (Tamim et al. 2008; Hallas et al. 2009; Pottegård et al. 2016; Kahan et al. 2018; Pottegard et al. 2016). 4 studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively (Tamim et al. (2008), no analysis reported; Pottegard et al. (2016a), OR= 1.01 (0.86-1.19) for any use, OR= 1.06 (0.84-1.34) for >5 years use; Kahan et al (2018), standardized incidence ratio= 0.93(0.6-1.38) for male subjects and 1.25 (0.91-1.69) for female subjects; Pottegard et al. (2016b), OR = 1.3 (0.7-2.1)). Hallas et al. (2009) showed a slight increase in cancer prevalence in subjects with long term exposure to lithium (Hallas et al. (2009), OR = 1.19 (1.03-1.39)).

# Cimetidine

3 cohort studies assessed the association between cimetidine use and cancer prevalence (Velicer, Dublin, and White 2006; Moller et al. 1989; Rossing et al. 2000). The study by Moller et al. did not include a control group (Moller et al. 1989). The remaining two cohort studies investigated gastrointestinal, breast and prostate cancer risk and found no significant increase in cancer risk in the groups exposed to cimetidine in comparison to controls (Velicer et al. (2006), RR = 0.97 (0.61-1.53); Rossing et al. (2000), RR= 0.9 (0.8-1.1) for breast cancer risk in women and RR = 0.7 (0.6-0.8) for prostate cancer in men). Rossing et al. found a slightly increased risk of prostate cancer in a subgroup of men who had filled >21 prescriptions of cimetidine, (Rossing et al. (2000), RR = 1.4 (1.0- 1.9)).

5 case-control studies assessed the association between cimetidine use and cancer prevalence (Mathes et al. 2008; Coogan et al. 2005; Holly and Lele 1997; Schumacher et al. 1990; Møller, Nissen, and Mosbech 1992). In all studies, cimetidine exposed

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individuals showed no significant difference in ratio compared to controls (Coogan et al. (2005), OR=0.9 (0.6-1.2); Holly et al. 1997, OR = 0.39 (0.17-0.89); Mathes et al (2008), ductal carcinoma, ever use: OR= 1.1 (0.8-1.5); >2 years use, 0.9 (0.5-1.5); Moller et al. (1992), no analysis reported; Schumacher et al. (1990), OR= 2.1 (0.7-6.3)). Lastly, a cohort study and a surveillance study conducted by Colin Jones et al. showed no increased cancer prevalence after cimetidine exposure (Colin-Jones et al. 1991, Colin Jones et al. 1983).

#### Haloperidol

A cohort study by Wang et al. assessed the association between haloperidol use and breast cancer prevalence, including a total of 46,269 women. A breast cancer incidence of 0.052% (1228 cases in 237242 person-years in control group and 240 cases in 46269 person years in haloperidol group) was found in both exposed and unexposed groups, indicating no significant increase in breast cancer incidence in women exposed to haloperidol compared to unexposed women (Wang et al. 2002).

Additionally, 3 case-control studies assessed the association between haloperidol use and cancer prevalence. A case-control study by Friedman et al. found a potential negative association between haloperidol use and prostate cancer risk, compared to controls depending on duration (Friedman et al. 2020, at >2 years of use, OR = 0.54 (0.20–1.44), at >1 year of use OR = 0.32 (0.12–0.84), at <1 year of use, OR = 0.69 (0.48–0.99)). Another case-control study by Hsieh et al. found a reduced risk of gastric cancer associated with haloperidol use (Hsieh et al. 2019,OR = 0.25 (0.14- 0.46)). A third, population-based case-control study by Chen et al. assessed the risk of endometrial cancer after exposure to haloperidol and other antipsychotics. For haloperidol, an increase of endometrial cancer after exposure to haloperidol was found (Chen et al. (2023), OR= 1.75 (1.31-2.34)).

Three database studies assessed the association between haloperidol use and cancer prevalence. The database study by Maeshima et al. using the Japanese adverse drug event database showed no increased risk of breast cancer in women exposed to haloperidol (Maeshima et al. (2021), ROR = 0.49 (0.07-3.51)). However, the study by Lertxundi et al. using the European pharmacovigilance database showed a possible increased risk of pituary tumors of subjects exposed to haloperidol (Lertxundi et al. (2019), PRR= 7.0 (4.35-11.3)). Finally, a pharmacovigilance study using the adverse event reporting database from the U.S.A's food and drug administration by Szarfman et al. suggested a possible increased risk of pituary tumors in patients exposed to haloperidol (Szarfman et al. (2006), ARR= 5.6 (2.9-13)).

#### Olanzapine

Three case-control studies assessed the association between olanzapine use and cancer prevalence. A nationwide case-control study by Pottengard et al. assessed the association between olanzapine use and breast cancer prevalence. Breast cancer cases were verified by histology. This study found a slightly increased risk of estrogen receptor-positive breast cancer in subjects exposed to olanzapine, attributed to its prolactin

elevating properties when the study was only adjusted for age and gender (Pottegård et al. (2018), aOR= 1.30; 95% CI = 1.09-1.56)); however, in the fully adjusted model, no significant increase was found (aOR= 1.15; 95% CI= 0.9-1.47). Another case-control study by Hsieh et al. found a reduced risk of gastric cancer associated with olanzapine use (Hsieh et al. (2019), OR= 0.13 (0.05-0.35)). Lastly, the case-control study by Chen et al. found no increased risk of endometrial cancer after exposure to olanzapine (Chen et al. (2022), OR = 1.14 (0.56-2.30).

Three database studies assessed the association between olanzapine exposure and cancer prevalence (Maeshima et al. 2021; Lertxundi et al. 2019; Szarfman et al. 2006). The database study by Maeshima et al. showed no increased risk of breast cancer in women exposed to olanzapine (Maeshima et al. (2021), ROR= 0.51 (0.07-3.51)). However, the database studies performed by Lertxundi et al. and Szarfman et al. suggested an increased risk of pituary tumors of subjects exposed to olanzapine. (Lertxundi et al. (2019), PRR= 2.53, (1.57-4.1); Szarfman et al. (2006), ARR=2.3 (1.4-3.7)).

#### Clozapine

One cohort study by Tiihonen et al. assessed the risk of developing hematologic malignancies after exposure to clozapine. A significant, dose dependent, increased risk of hematologic malignancies was found (Tiihonen et al. (2022), aOR= 3.35 (2.22-5.05) for >5000 defined daily dose cumulative exposure).

Three case-control studies assessed the association between clozapine exposure and cancer prevalence. The case-control study by Hsieh et al. assessed the association between clozapine exposure and cancer prevalence and found a reduced risk of gastric cancer associated with clozapine use (Hsieh et al. (2019), OR = 0.35 (0.13-0.97)). The case-control study by Chen et al. found no increase in endometrial cancer risk after exposure to clozapine (Chen et al. (2022), OR = 1.14 (0.56–2.30)). The case-control study by Tiihonen et al. found an increased risk of hematologic malignancies after exposure to clozapine (Tiihonen et al. (2022), aOR = 2.94 (2.07-4.17)). Interestingly, no significant difference for non-hematologic malignancies were found (Tiihonen et al. (2022), aOR for clozapine: 1.47 (1.25-1.47); for other antipsychotics: 1.30 (1.15-1.47)).

Additionally, four database studies assessed the association between clozapine exposure and cancer prevalence. Two database studies by Szarfman et al. and Lertuxi et al., assessed the association of clozapine and pituary tumor prevalence. For clozapine, both studies showed no significant increase in pituary tumor prevalence in subjects exposed to clozapine (Szarfman et al. (2006), ARR= 0.9 (0.4-1.7); Lertxundi et al. (2019), PRR=0.98 (0.5-1.8)). Two pharmacovigilance studies by Chrétien et al. and Dawson et al. assessed the risk of developing hematologic malignancies in subjects exposed to clozapine, due to the risk of severe haematologic side-effects when using clozapine. In the first study, clozapine exposed individuals had a significantly increased prevalence of leukemia (Chrétien et al. (2021), aOR = 3.54 (2.97-4.22) and malignant lymphoma, aOR=9.13, (7.75- 10.77) compared to controls). In the second study an excess of

hematological cancers in subjects exposes to clozapine was reported, indicating a possible increase in cases (Dawson et al. (2023), no analysis performed).

#### Discussion

#### Interpretation of the results/summary of main results

The aim of this review was to assess the risk of cancer development after the use of drugs that activate the Wnt pathway in humans. 43 observational studies (**Table 2**) analyzing the risk of cancer of 6 different drugs that have known Wnt activating properties were included in this systematic review. The drugs assessed in this review were VPA, lithium, cimetidine, haloperidol, olanzapine, and clozapine. Most of the included studies showed no increase in cancer prevalence after being exposed to Wnt activating drugs. These results suggest that using medication that activates the Wnt pathway in patients does not elevate cancer prevalence.

A few included studies showed an increase in the prevalence of malignancies after usage of Wnt activating drugs. Interestingly, the included studies that showed an increase in cancer prevalence reported increased cancer prevalence for specific cancer types; there was not a systematic increase in cancer risk. The study by Zaidan et al., showed an increased risk of developing solid renal tumors after a median of 20 years of lithium exposure. However, as lithium is known to be nephrotoxic, and no systemic increase in cancer risk was observed, this increase in cancer prevalence could be attributed to direct toxicity, rather than the activation of the Wnt pathway (Zaidan et al. 2014). Chen et al. found an increased risk of endometrial cancer after exposure to haloperidol, attributed to antipsychotic-induced hyperprolactinemia, which is a common side-effect of antipsychotics, and not to the Wnt pathway activation. Of note are both olanzapine and clozapine, which also activate the Wnt pathway, but showed no increase in endometrial cancer risk (Chen et al. 2022).

One study (which had many confounders and a high risk of bias), found an increased prevalence of gastric cancer in patients that had used cimetidine for gastric ulcers compared to the general population (Colin Jones et al. 1983). No other included studies reported an increased cancer risk after cimetidine exposure. Therefore, it is not likely that cimetidine is carcinogenic. In this context, patients with gastric ulcers are already at a higher risk of developing gastric cancer (Søgaard et al. 2016). A better control for this study would have been patients with gastric ulcers and no cimetidine use.

Lastly, and most notably, multiple studies found an increased prevalence of hematologic malignancies in subjects that were exposed to clozapine (Chrétien et al. 2021, Dawson et al. 2022, Tiihonen et al. 2023). Clozapine is well-known as the first second generation (atypical) antipsychotic and gold standard drug for treatment-refractory schizophrenia, but it has many adverse effects. Agranulocytosis is a relatively common and well-known side-effect of clozapine (Legge and Walters 2019). Bone marrow toxicity has been described

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in *in vitro* studies (Pereira and Dean 2006). The pathogenesis of clozapine-induced agranulocytosis or bone marrow toxicity is still not clear; however, it is unlikely to be Wnt associated. Multiple alternative hypotheses have been described (Legge and Walters 2019), all non-related to the Wnt pathway activation. In the case-control study performed by Tiihonen et al., they reported no differences in non-hematological cancer risk for clozapine in comparison to other antipsychotic drugs (Tiihonen et al. 2022). Based on available data, we can conclude that subjects exposed to clozapine are at an increased risk of hematologic cancers, due to direct bone marrow damage, unrelated to its Wnt pathway activating properties. The fact that the increased cancer risk in patients exposed to clozapine has only been found in hematological malignancies and not in solid tumors supports this hypothesis.

In addition to cohort and case-control studies, multiple pharmacovigilance/surveillance studies were included in this systematic review (Table 2). The pharmacovigilance/surveillance studies by Lertxundi et al. and Szarfman et al. showed an increased risk of developing pituary tumors after being exposed to the antipscyhotics haloperidol and olanzapine (Lertxundi et al. 2019, Szarfman et al. 2006). Nonetheless, this risk was attributed to antipsychotic-induced hyperprolactinemia, which is a common side-effect of antipsychotics, and not to the Wnt pathway activation. None of the included studies showed an increased risk of non-pituary malignancies. Therefore, we can conclude the increase in cancer risk is not caused by the Wnt activating properties of these drugs.

# Strengths and weaknesses of the review

We assessed the cancer risk of multiple drugs with laboratory proven Wnt pathway activation. Most of the included drugs activate the Wnt pathway through GSK3-Beta inhibition (**Table 1**) (Furuta et al. 2017; Sutton et al. 2007). Since the activation of Wnt is not their main therapeutic target, the level of Wnt activation may differ between various drugs. However, to assess all data available on the prevalence of cancer after usage of drugs that activate Wnt, we included all available mechanisms to Wnt activation. This study therefore included all papers available.

This systematic review included a complete search of all data available until November 17<sup>th</sup>, 2023. Moreover, bias was minimized by using two independent authors in the screening process.

# Strengths and weaknesses of the included studies

In this review, 43 studies were included, adding up extensive data on multiple drugs activating the Wnt pathway. The included studies showed a wide variety in risk of bias and methods, which leads to limitations in drawing conclusions. The main limitation is the drugs that were assessed in the included studies of this review. These drugs activate the Wnt pathway, but they were not specifically designed and used for their Wnt activating properties. These drugs have been in use since the 1950's and their Wnt activating properties have been described only in the last 30 years, mainly in *in vitro* experiments.

Novel Wnt activating drugs, like CHIR99021 (Yoshida et al. 2019), have been produced in the past few years. However, given that these drugs have not been used clinically, their risk is not clear and has to be assessed in the future. Furthermore, included studies had considerable missing data, including data to assess dose-related cancer risk, such as duration of treatment and used dosages. In most articles, Wnt activating properties were not discussed. Finally, there were no randomized controlled trials included in this review; only observational studies were included which are by design more at risk of bias due to the lack of randomization.

### Authors conclusions

### Implications for future research

As previously discussed, various applications are being researched for both activating and inhibiting the Wnt pathway. Cancer risk, however, remains a big concern (P. Huang et al. 2019). The results from this systematic review show that, at least for the included compounds in the currently used systemic dosage, cancer prevalence does not significantly increase. Therefore, based on this data we can conclude that compounds activating the Wnt pathway are, regarding cancer risk, a safe option. Still, the risk of bias of the included studies needs to be taken in consideration before taking this conclusion into medical practice. For that reason, further research on higher dosages, local administration and drugs specifically designed to induce Wnt activation should determine whether the activation of the Wnt pathway is indeed a safe treatment option with regards to cancer risk.

In the regenerative therapy field, Wnt activation is a promising agent for future treatment opportunities. Based on the data in this review, we can conclude that Wnt activation by the assessed compounds leads to no increased cancer risk. Therefore, further research into Wnt activation as a treatment option should be explored.

# Registration

The full version of this systematic review is pending for PROSPERO registration. Prospero ID: 2861

# Author Contributions

**Conceptualization:** AA, NS-C, LVS. **Methodology**: AA, IS. **Formal analysis**: AA, NS-C. **Investigation**, AA, SB, NSC. **Resources**: RS, IS, LVS. **Writing – Original draft**: AA, NS-C. **Writing- Review and Editing**: RS, IS, LVS. **Visualization**: AA, NS-C. **Supervision**: NS-C, IS, LVS. **Funding acquisition**: RS, LVS.

# Data statements

The data will be available upon reasonable request.

BMJ Open: first published as 10.1136/bmjopen-2025-103296 on 30 May 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES).

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# **Conflicts of Interests**

The authors declare no conflicts of interest

# Funding

This research was supported by Het Heinsious Houbolt fonds and Open Science Competition XS.

Aknowledgements

The authors aknowledge the Department of Otorhinolaryngology and Head & Neck Surgery of the UMC Utrecht.

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# Table 1. Mechanisms of action of all drugs included

Study	Mechanism of action	source
Cimetidine	GSK3beta inhibition	https://www.oncotarget.com/article/15206/text/
Clozapine	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin	https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.147 1-4159.2007.04527.x
Haloperidol	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin	https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.147 1-4159.2007.04527.x
Lithium	GSK3beta inhibition	https://www.oncotarget.com/article/15206/text/
Olanzapine	GSK3beta inhibition	https://www.oncotarget.com/article/15206/text/
Valproic acid	GSK3beta inhibition	https://www.oncotarget.com/article/15206/text/

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2 3 4	Appendix: Compounds in search string.
5	AR-A014418
6 7	AZD-1080
8 9	Chir-99021
10 11	CHIR98014
12 13	Cimetidine
14 15	FX-322
16 17	Gemifloxacin
18 19	Hydroxychloroquine
20 21	Lithium
22 23	LY2090314
24 25	Olanzapine
26 27	SB216763
28	TDZD8
29 30	Tideglusib
31 32	TWS119
33 34	TWS119
35 36	Hydroxychioroquine   Lithium   LY2090314   Olanzapine   SB216763   TDZD8   Tideglusib   TWS119   TWS119   Valproic acid
37 38	
39 40	
41 42	

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Table 2. Data extraction and results table for cohort studies on the use of VPA

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	/bmjopen-2025-103296 on d by copyright, ingluding f Analysis (95	Increase in cancer prevalence	Exposure duration	Risk o bias verdio
Chavez	2020	USA	Psychiatric	kaiser permanente consortium	92.6 per 100.000 person years	64 per 100.000 person years	ling foo HR = 0.64 (0.51-0.79 Ense Ense	No, decreased risk	Subgroups, up to >12 fills	Good
Chia lin	2018	Taiwan	Bipolar disorder	patients treated with anticonvulsants who did not use vpa	76/2663 (2.9%)	66/2663 (2.5%)	y 2025. Downloaded s related to text and 1(0.7-1.3)	No	Subgroups (<1 year, <3 years, >3 years)	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	aded from h 0.848 (0.563-1.船石 (ABB m h	No	cDDD (communitive daily dose of up to 215 days	Good
Каае	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any use: BCC 1.3(21), CMM 1(0.8-1.3), MC 1.2(0.2-8.7), SCC 23(11- 1.6) Per 5 years of use: BCC 1.1 (0.9-1.4); CMM 1 99 (35- 1.5) MCC No data, CC 0.8 (0.5-1.4)	No dose response	Risk per 5 years of exposure calculated	Good
Kang	2014	USA	Phsychiatric or neurologic disease	Smokers, never used VPA	9957/412717 (2.41%)	491/26911(2.58%)	lung (0.96), Head مقتط مودk (0.68), prostate (0.97), دهاده and rectum (0.9), هامطود (0.93) وو کې	No	>1 year (<1 year excluded)	Goo
Singh	2011	UK	Neurologic	UK general practice database; Unexposed to VPA	4.56 (4.19–4.96) /1000 person years n= 551	5.11 (4.37–5.98)/1000 person years n=155	(0.93) o 225 o 225 es: at Ag Rate ratio = 1.18 (0.96–1946) Ce Bi	No	>5 years, subgroup	Goo
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.877 (0.642-1.032)	No	>180 days	Goo

1	e 29 of 48					BMJ Op	oen	/bmjopen-2025-1 1 by copyright, in		
2 3 4	Table 3. Data ext	raction and Year	l results table Location	for non-cohort Indication for use	studies on the use Control condition	e of VPA Controls	Cases	င် ဥ Anaမှုsis 25%)	Increase in cancer prevalence	Risk of bias verdict
5 6 7 8	George	2023	Sweden	Antiepileptic	Matched controls	766 without cancer and exposed to VPA / 156036	117 patients with cancer exposed to VPA /31474	OR (95% (8)) 0.85 (0.800	no	Good
9 10 11 12 13	Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	or elated with Superior OR = 1.56) OR = 1.56)	No	Good
14 15 16 17 18	Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	x	x	and dead fit shown OR of Vaa minitigen	No	Good article, however, not all data on VPA available
19 20	Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	x	х	0.62 (@ 42-6 92) OR	Decrease	Good
21 22 23	Stritzelberger	2020	Germany	Neurologic	Epilepsy without cancer	21.0% of non cancer cases used VPA	21.5% of cancer cases used VPA	mjop0 Al traping,	No	Poor
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45				Fc	or peer review only -	http://bmjopen.b	mj.com/site/about/guideli	j.com/ on June 8, 2025 at Agence Bibliographique de and similar technologies.		

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Ingrease in Fanger pravalence	Exposure duration	Risk of bia verdict
Asgari	2017	USA	Ever exposed	Kaiser permanente consortium	14008 (92.5 per 100,000 person years)	48 (67.4 per 100,000 person years)	HR unadjusted = 0.68 (0.51-0.90); HR adjusted: 0.77 (0.58-102)	on 30 Mase g for uses No ses	<2 years, 2-5 years, >5 years	Good
Chia lin	2018	Taiwan	Bipolar disorder	Patients treated with anticonvulsants who did not use lithuim	48/1850 (2.6%)	26/925 (2.8%)	1(0.6-1.6)	5. Download temere Super tred to text a	Subgroups (<1 year, <3 years, >3 years)	Good
Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	19/609 (3.12%)	OR=1.19 (0.71- 2.01)	2025. Downloaded from http://b eignemene Superieur (ABES) . related to text and data mining,	37% treated for > 5 years; 26.4% treated <2 years	Fair - goo methodol groups t small.
George	2019	USA	Antiphysicotic medication	Postmenopausal women not treated with lithium	10079/155095 (6.5%)	18/326 (5.5%)	0.92 (0.58-1.46)	mjopen.bn N Al training	! - no acces	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	6 patients (1.6%)	0.426 (0.186- 0.975)	and Stecrease	cDDD (communitive daily dose of up to 215 days	Good
Kessing	2015	Denmark	Psychiatric	Randomly selected sample from Danish population	Total amount of subjects: 24.272	12,961/ 1.500.000 (0.86%)	Trend test: HR = 1.01 (0.97-1.05)	l June 8,2025 at. ≥ lar technologies.	Number of prescriptions up to 60 (= up to 10 years)	Good
Martinsson	2016	Sweden	Psychiatric	General population compared to Bipolar disorder (with and without lithium)	166,443 (6.4%)	142 (5,9%)	1.04 (0.89-1.23)	Agence	unclear, 'high'	Good
Zaidan	2014	France	Bipolar disorder	Matched (EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	p=0.04	Bibliographique de Ye	>20 years lithium exposure	Poor

Risk of bias verdict

Poor

Poor

Good

Good

Poor

Table 5. Data extraction and	d results table for case-contro	l studies on the use of lithium
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1 2	Table 5. Data	extractio	on and resul	ts table for ca	ase-control studies on the use	e of lithium		jht, i	5 5 7
3 4	Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	lncrease in cancer
5 6 7 8	Hallas	2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	1.19 (1.03-1.39) 8 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	shown, not the main question)
9 10 11 12	Kahan 2018 Israel Bipolar disorder		All members if LHS (Health Expected cancer cases Lithium insurance company) cases: 68 group: 61.09			standardize incidence ratio 0.93(0.6-1.38); ferral 1.25 (0.91-1.69	No No		
13	Pottengard	2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	1.01(0.86-1.12)	No
14 15	Pottengard	2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	1.01(0.86-1.12) OR = 1.3 (0.7-2017	•
16 17 18 19 20	, 3 Tamim 2008 Canada Psychiatric 9		69 cases lithium (0.9%); and 257			r (ABES) - rata mining, N.A.	No		
21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44					For peer review only - ht		.com/site/about	o, 2023 at Agence bibliographique de hnologies.	

Table 6. Da	ata extract	ion and result	s table for coho	ort studies on the	e use of cimetidine	BMJ Open e		in Womjopen-202 Vor 1 by copyright, In		
Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	ht D Lincrease in C Concer Corregalence	Exposure duration	Risk of bias verdict
Moller	1989	Denmark	Gastro- intestinal	No control, na	tional incidence		RR= 1.5 (p<0.001)	ng of es	not specified	Poor
Rossing	2000	USA, western Washington State	Gastro- intestinal	All males/females in the area	Total cohort = 48.512 users. Cases not shown	267 cimetidine Cases	0.9 (0.8–1.1)	20	not specified	Good, however not all data shown.
/elicer	2006	USA	Gastro- intestinal	Victims and lifestyle cohort	478 (1.8%) (incidence=7.6)	20 (1.6%)(incidence is 8.5)	RR= 0.97 (0.61- 1.53)	o Dowfiloade nent Super d to text an	not specified	Fair
						open.bmj.com/site/ak		2025 at Agence Bibliographique de nologies.		

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#### BMJ Open

Page 33 Tal 1 2		action and resu	ults table	e for surveil	llance and ca	ase-control s	BMJ Open studies for the use		d by copyright, including	Vbmjopen-2025-1 1 by copyright, in		
3 4 5	Type of study	Study	Year	Location	Indication for use	Control condition	Controls	Cases	including f	95%) Shalysis (95%)	Increase in cancer prevalence	Risk of bias verdict
6 7 8	Surveillance	Colin jones	1991	UK	Gastro- intestinal	x	x	111/9928 (1.1%)	for use	Control group!	No	Poor
9 10 —	Surveinance	Colin jones	1985	UK	Gastro- intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	is rela	not done ==0.9 (0.6-1.2)	No	N/A
10 11 12		Coogan	2005	USA	Gastro- intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	ted to	B=0.9 (0.6-1.2)	No	Poor
13 14 15 16	Case-control	Holly	1997	USA	Gastro- intestinal	Never use	х	х	t Superiour of text and da	<b>b</b> =0.9 (0.6-1.2) 0.39 (0.17-0.89)	Decrease	Poor
17 18 19 20 21 22		Mathes	2008	USA	Gastro- intestinal	Never users	n= 1390, 1136 (92.5%) unexposed; 92 5(7.5%) ever use; 36 (2.9%) > 2 years	Ductal carcinoma: n=1148; 939 (92.1%) never use; 81 (7.9%) ever use; 27 (2.6%)>2 years of use	Ever use 1.5); Loguda 1.6); >2 years (0.5-1.5) aobt	al carcinoma:OR= 1.1 (0.8- carcinoma OR = 1.0 (0.7- use ductal carcinoma, 0.9 ar carcinoma, 1.1(0.6-1.9)	No	Fair
23 24		Moller	1992	Denmark	Gastro- intestinal		d controls Group	101	<b>()</b>	= 2.1 (0.7-6.3)	No	Poor
25 26		Schumacher	1990	USA	gastro- intestinal	Non users	x	x		21 (95% Cl = 0.7-6.3)	No	Poor
<ul> <li>27</li> <li>28</li> <li>29</li> <li>30</li> <li>31</li> <li>32</li> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> </ul>					For peer re	view only - h	ttp://bmjopen.bmj.	com/site/about/guide	hologies.	on lune & 2025 at Agence Riblingraphique de l		

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Table 8. Data	extraction a	nd results ta	ble for cohort stu	udies on the use		l Open lozapine, and olanzapin	/bmjopen-2025-10329، o d by copyright, includ g Analysis e		
Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence		Increase in cancer prevalence	Risk of bias verdict
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	ං 30 HR = 1.05 හි බදු 1.21 හි යෙන	No	Good
Tiihonen	2022	Finland	Clozapine (schizofrenia)	matched controls (schizofrenia patient withot cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted Officer 255 (2.22-5.05) and a second secon	Yes, hematologic	Good
						n.bmj.com/site/about/gui	8, 2025 at Agence Bibliographique de chnologies.		

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	Table 9. Data	extractior	and results	table for case-o	control studies on	the use of haloperio	dol, clozapine, and olar	nzapine vy en v		
1 2 3	Study	Year	Location	Drug of interest	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysismic and a second secon	Increase in cancer prevalence	Risk of bias verdict
4 5 6				Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	(1.31-2,34)5	yes	
7 8	Chen	2022	Taiwan	Olanzapine	Matched controls	63/37908	13/9502	OR (95% ČI) 0 <b>3</b> 2 (0.38– <b>2</b> 35)	no	Good
9 10				Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% U)01 4 (0.56-49)02	no	
11 12	Fui o duce o	2020		Uslansvidal	Not treated with	39553/1962602 (2.0%)	4/352 (1.1%)	OR = 0.54 (020 5.44)		Cood
13 14	Friedman	2020	USA	Haloperidol 🧹	haloperidol	576 2008	4/576 (0.7%) 30/2008 (1.5%)	OR = 0.32 (0 4 5 8 8 4) OR = 0.69 (0 4 5 9 .99)		Good
15 16				Clozapine	Non-gastric cancer	92 (0.06%)	4 (0.01%)	OR = 0.35 (6137)		
17 18 19	Hsieh	2019	Taiwan	Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (G100 46)	No, decrease	N/A
20 21				Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (0-05 )	No, decrease	
22 23 24 25	Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted O 1: 3.30 (1.09-1556) Adjusted O 2: 1.15 (0.9-137)	No in fully adjusted model (2), yes when only adjusted for age and gender	Good
26 27 28 29 30	Tiihonen	2022	Finland	Clozapine	No cancer	3734 matched controls (9.9used clozapine%)	375 cases; 19,5% used clozapine.	aOR = 2.94 (33.0751.17)	Yes, hematologic cancers	Good
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45					For peer review o	only - http://bmjopen.	bmj.com/site/about/gui	ne 8, 2025 at Agence Bibliographique de I technologies. delines.xhtml		

BMJ Open Table 10. Data extraction and results table for pharmacovigilance and database studies on the use of haloperidol, clozapine and objective and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol and batabase s

Study	Year	Drug of interest	Control condition	Type of cancer	Cancer risk Wnt group = prevalence	rright, includ	Increase in cancer prevalence	Risk of bias verdict
		Clozapine	х	Pituary tumor	17 cases	∄RR 0.98 (0.5-1.8)	No	
Lertxundi	2019	Haloperidol	х	Pituary tumor	11 cases	₫ RR = 7.0(4.35-11.3)	Possibly	N/A
		Olanzapine	х	Pituary tumor	17 cases	<b>₽</b> ₽.53 (1.57-4.1)	Possibly	
		Clozapine	х	Pituary tumor	4 cases	<b>2</b> ́A <b>3</b> ́K = 0.9 (0.4-1.7)	No	
Szarfman	2006	Haloperidol	х	Pituary tumor	9 cases	a/a 25 5.6 (2.9-13)	Possibly	N/A
		Olanzapine	x	Pituary tumor	11 cases	2.3 (1.4-3.7)	Possibly	
	2224	Clozapine	x	Hematologic malignancies	275	aR	Possibly	
Chretien	2021	Olanzapine	x	Hematologic malignancies	68	ak 0.88 (0.66- 1.16)	No	N/A
Maeshima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1 60049 (0.07, 3.51) ROR	No	N/A
Maestiinia	2021	Olanzapine	x	Benign and malignant breast cancer	1825	ຊີ (ວິດ 2 ສາຫຼີ (0.07, 3.51) ROR ສາຜູ້	No	N/A
Dawson	2023	Clozapine	x	Hematological	104/384	excess f.hematological cancers in people expozed to clozapine	Possibly	
				Neoplasm	61/384	jope	No	
				Lung	50*384	open.bm training,	No	
				Breast	37/384	jų, s	No	
				Colorectal	28/384	and con	No	
				Brain	18/384	sim o	No	
				Skin	17/384	pen.bmj.com/ on June 8, 2025 at raining, and similar technologies	No	NI / A
				Esophagogastric	11/384	tec	No	N/A
				Pancreatic	10/384		No	
				Urological	9/384		No	
				Testicular	8/384	jies	No	
				Hepatic	7/384	Ag	No	
				ENT	6/384	enc	No	
				Gynecological	<5/384	2025 at Agence Bib vologies.	No	
				others	14/384		No	
			For peer review	/ only - http://bmjopen.bmj.cor	m/site/about/quidelin	iographique de l		

-	e 37 of 48 able 11 C	ritical a	opraisal table fo	or cohort studi	es on the use of VPA	BM.	J Open	/bmjopen-2025-10329 d by copyright, includ		
1 2								/bmjopen-2025-103296 1 by copyright, includir		
3 4						Selection (max 1 star)		0329( cludi		Outcome nax 1 star)
5 6 7 8 9	Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	- Comparibility of cohorts م (max 2 s	Ascertainment of outcome	Long enough follow up
10 11	Chavez	2020	Retrospective cohort		*	*	*	v 2025. Dowr seignement \$ s related to to * * * * *	*	*
12 13	Chia lin	2018	retrospective cohort study	*	*	*	*		*	*
14 15	Huang	2016	retrospective cohort study	*	*	*	*	aded and *	*	*
16 17 18	Каае	2010	population- based cohort study	*	*	*	*	l from http://b ur (ABES) . data mining, * * *	*	*
19 20	Kang	2014	retrospective cohort study		*	*	*	ing, Al *	*	*
21 22 23 24	Singh	2011	cohort study	*	*	*	*	http://bmjopen.bmj.com/ ES) - nining, Al training, and si * * * *	*	*
24 25 26	Yang	2022	Nationwide cohort	*	*	*		and si *	*	*
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42								m/ on June 8, 2025 at Agence Bibliographique de l similar technologies.		
43					For peer review of	only - http://bmjope	n.bmj.com/site/about/guide	elines.xhtml		

44 45 46 Adequace Verdict

Good

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ole 12. Critical	apprais	al table for cas	e control studi	es on the use of <b>\</b>		IJ Open	d by copyright, including Comparibility of a set and	/bmjopen-2025-103296			Page 38
					Selection nax 1 star)		ht, inclu	025-103	Outcome (max 1 sta		_
Author	Year	Type of study	Representati tveness of cohort	Selection of non- exposed cohort		Demonstration that outcome of interest was not present at start of study	cases abd controls of (max 2 stars) ຜູ້	n Asscertain Asscertain Ament of Moutcome	Long enough follow up	Adequace of follow up	Verdic
George	2023	case-control study	*	*	*	**	** to	* * 19. Dow	*		Good
Hallas	2009	case control	*	*	*	*	** text	Sul *	*		Good
Kristensen	2019	nested case control study	*	*	*	**	* and data minin	* aded from http: perieur (ABES)	*		Good, howeve not all data available
Salminen	2016	case-control study	*	*	*	* *	ig, Al t	* //bmjo	*		Good
Stritzelberger	2020	Nested case control (from cohort?)	High risk of bia	s, not the aim of th	e study and not al	l data shown	raining, a	pen.bmj.c			Poor
Tilhonen	2022	case-control study	*	*	*	*	nd sim	* • • •	*		Good
				For peer review or	nly - http://bmjope	en.bmj.com/site/about/		* * * * * * * * * * * 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l eignement Superieur (ABES)			

39 of 48 able 13. Critica	l apprais	al table for coh	nort studies on the use	e of lithium		U Open		vunjepen-∠ d by copyrig				
								ht, inclu	000 7000			
Author	Year	Type of study	Representatitveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparibility o cohorts (max 2 stars)	Ens Ensuration Ensuration	hent of utcome	Long enough follow up	Adequace of follow up	Verdict
Asgari	2017	retrospectiv e cohort		*	*	*	**	lement ited to t	<b>7</b> *	*	*	Good
Chia lin	2018	retrospectiv e cohort study	*	*	*	*	**	Superieu ext and d	*	*		Good
George	2019	restrospectiv e cohort study	*	*	*	*	**	r (ABES) ata minin	*	*		Good
Huang	2016	retrospectiv e cohort study	*	*	*	*	**	g, Al train	*	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	**	ing, and s	*	*		Good
Martinsson	2016	Cohort nationwide		*	*	*	**	imilar	*	*	*	Good
Zaidan	2014	retrospective cohort study	Non applicable - Dat	a from coh	ort compared to	general population, e	xpressed as sta	5 0	0	idence ratio; s	small cohort	Poor
								Jence mmichiabuidae de				
	Author Asgari Chia lin George Huang Kessing Martinsson	AuthorYearAuthorYearAsgari2017Chia lin2018George2019Huang2016Kessing2015Martinsson2016	AuthorYearType of studyAsgari2017retrospectiv e cohortAsgari2017retrospectiv e cohortChia lin2018e cohort studyGeorge2019e cohort studyHuang2016e cohort studyHuang2016e cohort studyKessing2015(population based study)Martinsson2016Cohort nationwide	Author       Year       Type of study       Representatitveness of cohort         Asgari       2017       retrospectiv e cohort       *         Asgari       2017       retrospectiv e cohort       *         Chia lin       2018       e cohort       *         George       2019       e cohort       *         Huang       2016       e cohort       *         Huang       2016       e cohort       *         Martinsson       2016       Cohort nationwide       *         Zaidan       2014       retrospectiv cohort study       Non applicable - Dat	Author       Year       Type of study       Representativeness of cohort       Selection of non-exposed cohort         Asgari       2017       retrospectiv e cohort       *       *         Chia lin       2018       e cohort       *       *         George       2019       e cohort       *       *         Huang       2016       e cohort       *       *         Kessing       2015       (population based study)       *       *         Martinsson       2016       Cohort nationwide       *       *         Zaidan       2014       retrospectiv cohort study       *       *	Author       Year       Type of study       Selection (max 1 star)         Author       Year       Type of study       Representativeness of cohort       Selection of non-exposed cohort       Ascertainment of exposure         Asgari       2017       retrospectiv e cohort       *       *       *         Chia lin       2018       e cohort       *       *       *         George       2019       e cohort       *       *       *         Huang       2016       e cohort       *       *       *         Huang       2016       Cohort       *       *       *         Martinsson       2016       Cohort study       *       *       *         Martinsson       2016       Cohort nationwide       *       *       *         Zaidan       2014       retrospective cohort study       Non applicable - Data from cohort compared to       *	Author       Year       Type of study       Selection (max 1 star)         Author       Year       Type of study       Representativeness of cohort       Selection of non-of reposure of exposure of interest was not present at start of study         Asgari       2017       retrospectiv e cohort       *       *       *       *         Chia lin       2018       e cohort       *       *       *       *       *         George       2019       e cohort       *       *       *       *       *         Huang       2016       e cohort       *       *       *       *       *         Martinsson       2016       Cohort       *       *       *       *       *         Martinsson       2016       Cohort nationwide       *       *       *       *       *         Zaidan       2014       retrospective cohort study       Non applicable - Data from cohort compared to general population, e	Author         Year         Type of study         Representativeness of cohort         Selection exposed cohort         Demonstration that outcome of interest was not present at start of study         Comparibility cohorts was not present at start of study           Asgari         2017         retrospectiv e cohort         *	AuthorYearType of studyRepresentativeness of cohortSelection of cohortAscertaimmet of exposureDemonstration that outcome of interest was not present at start of studyComparibility of (max 2 stars) (max 2 stars)Asgari2017retrospectiv e cohort*** <td>Author         Year         Type of study         Representativeness of cohort         Selection (max 1 star)         Demonstration that outcome of interest start of study         Comparibility of (max 2 stars)         Comparibility of (max 2 stars)         Comparibility of (max 2 stars)         Comparibility</br></br></br></br></br></br></br></br></br></td> <td>Author       Year       Type of study       Representativeness of cohort       Selection of cohort       Ascertainment cohort       Demonstration that outcome of interest was not present at start of study       Comparability cohorts (mx 2 stars)       Comparability (max 2 stars)<td>Author     Year     Type of study     Representativeness of cohort     Selection of cohort     Ascertainment of exposed     Demonstration that outcome of interest start of study     Compatibility cohorts start of study     Operation operation     Adequace of follow up       Asgari     2017     retrospectiv e cohort     *<!--</td--></td></td>	Author         Year         Type of study         Representativeness of cohort         Selection (max 1 star)         Demonstration that outcome of interest start of study         Comparibility of (max 2 stars)         Comparibility of 	Author       Year       Type of study       Representativeness of cohort       Selection of cohort       Ascertainment cohort       Demonstration that outcome of interest was not present at start of study       Comparability cohorts (mx 2 stars)       Comparability (max 2 stars) <td>Author     Year     Type of study     Representativeness of cohort     Selection of cohort     Ascertainment of exposed     Demonstration that outcome of interest start of study     Compatibility cohorts start of study     Operation operation     Adequace of follow up       Asgari     2017     retrospectiv e cohort     *<!--</td--></td>	Author     Year     Type of study     Representativeness of cohort     Selection of cohort     Ascertainment of exposed     Demonstration that outcome of interest start of study     Compatibility cohorts start of study     Operation operation     Adequace of follow up       Asgari     2017     retrospectiv e cohort     * </td

e 14. Critical	l appraisal	table for case-c	ontrol studies on t	he use of li		MJ Open	rability ; including	/bmjopen-2025-103296		
				Selection (max 1 sta		-	rability , no stars) , no u	25- 103 (max 1 29		
Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	Comparability of	0	Non- response rate	Verdict
Hallas	2009	case control	*	*	*	*	** di	* 5. Dow ement	*	Good for VI bad for lithi
Kahan	2018	Case-control study from large database	Data from large da	tabase, scale	e non-applicable	, high risk of bias	text and	nloaded Superier		Poor
Pottengard	2016 (1)	Nationwide case control study	*	*	*	*	data min **	* from htt ur (ABES	*	Poor
Pottengard	2016 (2)	Case control study nationwide	*	*	*	*	** Al tr	* *	*	Good
Tamim	2008	Nested case- control	*	*	*	*	aining, an	* ven.bmj.co	*	Poor
							similar technologies.	m/ on June 8, 2025 at Agence Bibliographique de l		

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ige 41 of 48 Table 15. Critic	al apprais	al table for coh	ort studies on the use	e of cimeti		1J Open		של by copyright, includ <del>it</del>				
				Selecti	ion (max 1 star)		_	ight, incl		Outcome (max	1 star)	_
Author	Year	Type of study	Representatitvenes s of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability cohorts (max stars)	ova, 349 notay∡ Ensei yg√toruses n	scertain hent of utcome	Long enough follow up	Adequace of follow up	Verdict
) Moller	1989	Cohort	No control, high risk o	of bias				2025. Dow eignement related to t				Poor
Rossing	2000	Retrospective cohort study	*	*		*	**	Supe Supe	*	*	*	Good
Velicer	2006	Cohort study		*		*	**	aded from perieur (/ and data	*	*	*	Fair
						*		3, 2023 at Agence Bibilographique de nnologies.				

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				Selectio	on	Compa	aribility	ght, in	Outco	me	
Author	Year	Type of study	Adequacy of case definition	(max 1 s Represent ativeness of the cases			2 stars) Comparability cases and controls	by copyright, including to uses rel	C (max 1 s	Non- response rate	Verdict
Colin Jones	1985	case control study	No representativ	e outcome;	already had gas	strcic ulcers, only age and s	ex matched cor	nem@n atedigo			Poor
Colin Jones	1991	surveillance study	No control, NA					t Supe text a			N/A
Coogan	2005	Database study/case- control	*		*		**	nd data n	o short		Poor
Holly	1997	population- based case- control study				*	**	ES) . nining, A	*		Poor
Moller	1992	Case-control study						l training, a			Poor
Schumacher	1990	Case-control study	*	*			* *	and simila	60m/ 0n _		Moderate ri of bias?
						Definition of controls strcic ulcers, only age and s  *		technologies.	ine 8 2025 at Anence Riklingran		

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# BMJ Open

-	43 of 48 able 17. C	Critical a	appraisal table t	for cohort stud	ies on the use of halo		J Open , and olanzapine	/bmjopen-2025 d by copyright,				
1 2 3 4						Selection max 1 star)		includi		Dutcome nax 1 star)		
5 6 7 8 9	Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	- Comparia ility of coho t s and (max 2 s and a s and a s a s a s a s a s a s a s a s a s a		Long enough follow up	Adequace of follow up	Verdict
	Tilhonen	2022	cohort study	*	*	*	**	2025 elate *	*	*		Good
11 12 13	Wang	2002	Retrospective cohort	*	-	*	*	. Down ment S -	*	*	*	Good
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44							*	3, 2025 at Agence Bibliographique de Inologies.				

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# Table 18. Critical appraisal table for case-control studies on the use of haloperidol, clozapine, and olanzapine

				Selectio (max 1 st		-	Comparibility (max 2 stars) Comparibility o			me star)	
Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	cases and controls	₩ayō2025 Enseigne ses relate	certain hent of utcome	Non- response rate	Verdict
Chen	2022	Case-control study	*	*	*	*	**	Downloaded ment Superieu ed to text and c	*	*	Good
Friedman	2020	Case-control	*	*	*	*	**	paded fr	*	*	Good
<mark>Hsieh</mark>	<mark>2005</mark>	Database study/case- control						om http: (ABES) ata minin			Poor
Pottengard	1997	population- based case- control study	*	*	*	*	**	//bmjope g, Al trail	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	from http://bmjopen.bmj.com ur (ABES) data mining, Al training, and :	*	*	Good
							0 1	n/ on June 8, 2025 at Agence Bibliographique de l similar technologies.			

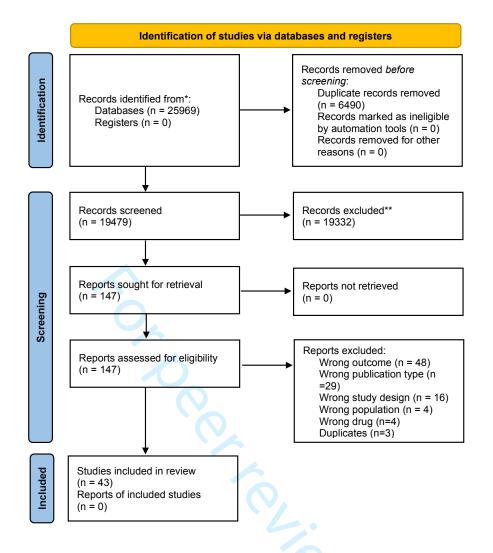


Figure 1: Article selection flow diagram. The identification of studies via databases and registers is presented above. The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion. The protocol was perfomed based on the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

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# Table S1: The search strategy

Database	Search string
PubMed	(Lithium[Title/Abstract] OR valpr*[Title/Abstract] OR tideglusib[Title/Abstract] OR AZD1080[Title/Abstract] FX322[Title/Abstract] OR Chir99021[Title/Abstract] OR TWS119[Title/Abstract] OR LY2090314[Title/Abstract] TDZD8[Title/Abstract] OR SB216763[Title/Abstract] OR CHIR98014[Title/Abstract] OR AR-A014418[Title/Abstract] Cimetidine[Title/Abstract] OR Olanzapine[Title/Abstract] OR 6-bromoindirubin-3'-oxime [Title/Abstract] OR Clozap [Title/Abstract] OR Haloperidol [Title/Abstract] OR Kenpaullone [Title/Abstract] OR L803mts [Title/Abstract] OR lithium[Me Terms] OR valproic acid[MeSH Terms] OR olanzapine[MeSH Terms] OR haloperidol[MeSH Terms] OR gsk3 inhib*[Title/Abstract] OR wnt acti*[Title/Abstract] OR wnt agon*[Title/Abstract] OR blastoma*[tw] OR cancer*[tw] OR carcinogen*[tw] OR carcinom*[tw] adenoma*[tw] OR anticarcinogen*[tw] OR blastoma*[tw] OR cancer*[tw] OR carcinogen*[tw] OR carcinom*[tw] carcinosarcoma*[tw] OR chordoma*[tw] OR hodgkins disease[tw] OR leukemi*[tw] OR hyphangioma*[tw] disease[tw] OR hodgkin's disease[tw] OR hodgkins disease[tw] OR leukemi*[tw] OR melanom*[tw] lymphangiomyoma*[tw] OR lymphangiosarcoma*[tw] OR mesonephroma*[tw] OR metasta*[tw] OR neoplas*[tw] OR neuroma*[tw] meningioma*[tw] OR oncolog*[tw] OR paraneoplastic[tw] OR plasmacytoma*[tw] OR precancerous[tw] OR sarcoma*[tw] OR teratocarcinoma*[tw] OR teratoma*[tw] OR tumor*[tw] OR tumor*[tw])
EMBASE	('lithium':ti,ab,kw OR 'valpr*':ti,ab,kw OR 'tideglusib':ti,ab,kw OR 'azd1080':ti,ab,kw OR 'fx322':ti,ab,kw OR 'chir99021':ti,ab,kw 'tws119':ti,ab,kw OR 'ly209314':ti,ab,kw OR 'tdzd8':ti,ab,kw OR 'sb216763':ti,ab,kw OR 'chir98014':ti,ab,kw 'ara014418':ti,ab,kw OR 'cimetidine':ti,ab,kw OR 'clanzapine':ti,ab,kw OR '6-bromoindirubin-3-oxime':ti,ab,kw 'clozapine*':ti,ab,kw OR 'haloperidol':ti,ab,kw OR 'kenpaullone':ti,ab,kw OR 'l803mts':ti,ab,kw OR 'gsk3 inhib*':ti,ab,kw OR 'v acti*':ti,ab,kw OR 'wnt agon*':ti,ab,kw OR 'beta catenin activ':ti,ab,kw OR 'l803mts':ti,ab,kw OR 'gsk3 inhib*':ti,ab,kw OR 'v acti*':ti,ab,kw OR 'wnt agon*':ti,ab,kw OR 'beta catenin activ':ti,ab,kw OR 'lithium'/exp OR 'valproic acid'/exp OR 'tideglusib'/ OR 'haloperidol'/exp OR 'olanzapine'/exp AND ('neoplasm'/exp OR 'neoplasm' OR adenoma*:ti,ab,kw OR anticarcinogen*:ti,ab, OR blastoma*:ti,ab,kw OR carcer*:ti,ab,kw OR carcinogen*:ti,ab,kw OR carcinom*:ti,ab,kw OR ((hodgkin* NEX disease):ti,ab,kw OR germinoma*:ti,ab,kw OR gonadoblastoma*:ti,ab,kw OR hepatoblastoma*:ti,ab,kw OR ((hodgkin* NEX disease):ti,ab,kw OR lymphom*:ti,ab,kw OR malignan*:ti,ab,kw OR neoplas*:ti,ab,kw OR neoroma*:ti,ab,kw nesenchymoma*:ti,ab,kw OR mesonephroma*:ti,ab,kw OR metasta*:ti,ab,kw OR neoplas*:ti,ab,kw OR neuroma*:ti,ab,kw nsclc:ti,ab,kw OR oncogen*:ti,ab,kw OR oncolog*:ti,ab,kw OR paraneoplastic:ti,ab,kw OR plasmacytoma*:ti,ab,kw tumour*:ti,ab,kw)
Cochrane	(Lithium OR valpr* OR tideglusib OR AZD1080 OR FX322 OR Chir99021 OR TWS119 OR LY2090314 OR TDZD8 OR SB216763 CHIR98014 OR AR-A014418 OR Cimetidine OR Olanzapine OR Clozapine OR Haloperidol OR Kenpaullone OR L803mts OR g inhib*OR wnt acti*OR wnt agon*OR Beta catenin activ*)
	AND
	(adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* germinoma* OR gonadoblastoma* OR hepatoblastoma* OR (hodgkin* NEXT/1 disease) OR leukemi* OR lymphangioma* lymphangiomyoma* OR lymphangiosarcoma* OR lymphom* OR malignan* OR melanom* OR meningioma* OR mesenchymor OR mesonephroma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*)

# PRISMA 2020 Checklist

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PRISM	/A 20	)20 Checklist	
Section and Topic	ltem #	Checklist item	Location where iten is reported
TITLE			
Title	1	Identify the report as a systematic review.	yes
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Yes
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Yes
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted identify studies. Specify the date when each source was last searched or consulted.	Yes
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	Yes
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how may device a screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	yes
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each epot, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, detate of automation tools used in the process.	Yes
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with act outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which study to collect.	Yes
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, and g sources). Describe any assumptions made about any missing or unclear information.	Yes
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, here ny reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Yes
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Yes
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the studies to decide which studies were eligible for each synthesis (e.g. tabulating the studies of the studies and comparing against the planned groups for each synthesis (item #5)).	Yes
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing sumpary statistics, or data conversions.	Yes
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Yes
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Yes
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Yes
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Yes
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting bias s).	Yes
Certainty	15	o Describe any methods used toeassesteoertainty (مدرمه/ttideoca)-in/the doody عاره/videoce/forcani outcome	Yes



# PRISMA 2020 Checklist

		BMJ Open BMJ Open	Page 48 of 48	
PRISM	/A 20	BMJ Open 920 Checklist		
Section and Topic	ltem #	Checklist item	Location where item is reported	
assessment				
RESULTS		in the second se		
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to t	Yes	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they ward cluded.	Yes	
Study characteristics	17	Cite each included study and present its characteristics.	Yes	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Yes	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) a structured tables or plots.	Yes	
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Yes	
syntheses	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary with the and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Yes	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Yes	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Yes	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis a sector	Yes	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Yes	
DISCUSSION				
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Yes	
	23b	Discuss any limitations of the evidence included in the review.	Yes	
	23c	Discuss any limitations of the review processes used.	Yes	
	23d	Discuss implications of the results for practice, policy, and future research.	Yes	
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Yes	
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Yes	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the eview.	Yes	
Competing interests	26	Declare any competing interests of review authors.	Yes	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Yes	
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		

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# **BMJ Open**

# A systematic review on cancer prevalence after exposure to Wnt activating drugs

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Journal:	BMJ Open
Manuscript ID	bmjopen-2025-103296
Article Type:	Original research
Date Submitted by the Author:	07-Apr-2025
Complete List of Authors:	aLKASHAF, AhmeD; University Medical Centre Utrecht Smith-Cortinez, Natalia; University Medical Centre Utrecht Fenton , Georgina; University Medical Centre Utrecht Bok, Sebastian; University Medical Centre Utrecht Stokroos, Robert; University Medical Center Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Stegeman, Inge; University Medical Center Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Straatman, Louise; University Medical Centre Utrecht, Otorhinolaryngology
Keywords:	Prevalence, Epidemiology < ONCOLOGY, ONCOLOGY





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A systematic review on cancer prevalence after exposure to Wnt activating drugs Ahmed Alkashaf<sup>a,#</sup>, Natalia Smith-Cortinez<sup>a,b,#</sup>, Georgina Fenton, Sebastian T. Bok<sup>a</sup>, Robert J. Stokroos<sup>a,b</sup>, Inge Stegeman<sup>a,b</sup>, Louise Straatman<sup>a,b,\*</sup> a Department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands. b UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Universiteitsweg 100. 3584 CG Utrecht, Netherlands \*Corresponding author #Shared first authorship Abstract **Objectives:** To assess whether treatment with drugs that activate the Wnt pathway leads to an increased risk of cancer. **Design:** Systematic review using PRISMA guidelines **Data sources:** PubMed, Embase and the Cochrane Library were searched through 1 November 2024. Eligibility criteria for selecting studies: All primary research articles reporting clinical studies, including observational and experimental studies were included in this review. All studies were eligible for inclusion if they included the exposure of interest, i.e. compounds which have been described to activate the Wnt pathway, and the outcome of interest, i.e. cancer prevalence. No language restrictions were performed. Data extraction and synthesis: This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The search string, objectives, and study protocol methods were defined before the study was initiated. **Results:** A total of 48 studies investigating drugs that activate the Wnt pathway (valproic acid, lithium, cimetidine, olanzapine, clozapine, haloperidol) were included in this systematic review. The results from this systematic review show that, at least for the included compounds in the currently used systemic dosage, cancer prevalence does not significantly increase. **Conclusions:** The current study found that the use of drugs that activate the Wnt pathway was not associated with an increased risk of cancer. As a promising agent in the regenerative therapy field, further research into Wnt activation as a treatment option should be explored. **Keywords:** Wnt activating drugs; cancer prevalence; lithium; valproic acid. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 

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List of abbreviations GSK 3, glycogen synthase kinase 3 HR, hazard ratio MDS, myelodysplastic syndrome OR, odds ratio RR, risk ratio SLE, systematic lupus erythematosus VPA, valproic acid Wnt, Wnt/Beta-catenin signaling pathway (emmony)

# 45 Introduction

The Wnt/ $\beta$ -catenin pathway is a signaling cascade that controls cell proliferation. cell polarity, and cell fate determination during embryonic development and tissue homeostasis (1). Wnt/β-catenin signaling is known to be involved in development of multiple tissues, including brain, eye, ear, spinal cord, bone cartilage among many others (2). In adulthood crucial roles in the function of intestine, bone and skin have been described for Wnt/β-catenin signaling (2). Wnts (the ligands that activate the Wnt/β-catenin signaling pathway) are growth stimulatory factors that ultimately lead to cell proliferation (Niehrs and Acebron, 2012). Importantly, dysregulated Wnt signaling has been associated with several diseases such as degenerative diseases (Nusse and Clevers, 2017), neurodegenerative disorders (3–5) schizophrenia (5), aging-related tissue fibrosis (6), autoimmune diseases (7) and many types of cancer (8–12). 

Currently, targeting the Wnt/ $\beta$ -catenin signalling pathway, either by activating or inhibiting it, is being researched as therapy for some types of cancer (13,14), neurodegenerative diseases (15–18), hair loss (19,20). When therapeutic agents target crucial developmental signaling pathways (such as Wnt, Notch, Hedgehog and bone morphogenic protein (BMP) pathways) serious and devastating effects on embryogenesis and carcinogenesis might arise due to increased cell proliferation. In line, continued activation of the Wnt pathway has been associated with therapy resistance in cancer patients and has been shown to promote self-renewal of cancer cells (21). Unfortunately, the effect of Wnt activation on cancer prevalence has not been consistently studied. In the last 15 years, common drugs used in the clinic have been described to activate the Wnt pathway (22,23). The most common Wnt activators used in the clinic are lithium and valproic acid (VPA), which have been used as treatment for psychiatric disorders since the 1960's (24-26). Besides, many novel therapeutic drugs have been synthesized specifically to activate Wht in the last 10 years and are used in the clinic (27). Many of these drugs activate the Wnt signaling pathway through the inhibition of glycogen synthase kinase 3 (GSK3) (28). This is one the most well studied mechanisms for activating the Wnt signaling pathway (28). 

There are many novel therapeutic drugs in development for clinical usage that activate the Wnt pathway. However, safety concerns regarding its activation remain (29). Therefore, we conducted a systematic review to address the association between the use of drugs that activate the Wnt pathway and prevalence of any type of malignancy in the clinic. Our aim was to assess whether treatment with drugs that activate Wnt leads to an increased risk of cancer.

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#### **Methods**

We evaluated all data available on clinical use of Wnt activators following the Prisma 2020 writing guideline for systematic reviews (30). PICO framework was used to improve the search strategy (31). The outcome of interest was the prevalence of any cancer, malignancy, or neoplasm, regardless of age, sex, and geographic location. The exposure of interest was any compound activating the Wnt pathway, regardless of indication, dosage and duration. An overview of the included compounds and their mechanism of action is available in Table 1. 

#### Search strategy

The final search was done on November 1<sup>st</sup>, 2024. PubMed, Embase and Cochrane databases were searched. All articles until November 1<sup>st</sup> were included in the search. On Embase, conference abstracts and reviews were removed. No further search filters were used. No language restrictions were applied. The search syntax consisted of names of medication with known Wnt activating properties used in the clinic combined with synonyms for 'cancer'. The full search strategy can be found in **Supplementary** Table S1. 

#### Article selection

All primary research articles reporting clinical studies, including observational and experimental studies were included in this review. Studies were eligible for inclusion if they included the exposure of interest, i.e. compounds which have been described to activate the Wnt pathway, and the outcome of interest, i.e. cancer prevalence. Patients of all ages were eligible for this study. No control group was required. Articles assessing compounds with no clear Wnt activating properties were excluded. Animal studies, in vitro studies and non-primary research articles like review articles and letters were excluded. Two independent reviewers (A.A., G.F. N.S-C, S.B.) screened title and abstracts of collected studies after duplicate removal for eligibility criteria. Discrepancies were resolved by discussion between the two reviewers until a consensus was reached. Full text screening was performed by two independent reviewers and disagreements were solved as above. Rayyan systematic review tool (32) was used to semi-automate the primary screening. 

#### Data extraction

A data extraction table was used to extract study characteristics and findings by two reviewers (A.A., N.S-C) with the software Microsoft Excel. Data extraction was performed by one reviewer and checked by another reviewer. Discrepancies were solved by discussion between the two reviewers until a consensus was reached. The data extraction table included the following information: Study, indication for intervention, population, age, geographical location, used Wnt activator, used control group, cancer prevalence and cancer type (Tables 2-10). Authors were contacted if data was not reported in the article or otherwise unavailable. 

- The methodological quality of included articles was assessed by two reviewers (AA. N.S-C) using the Newcastle Ottowa-Scale (NOS) for nonrandomized studies as a reference guide (33). Risk of bias assessment was performed by one reviewer and checked by another reviewer. Risk of bias in cohort studies was assessed for the following domains: selection bias, comparability of cohorts, and outcome (Tables 11 - 18). Results were expressed according to the reported ratios from the published studies. This includes percentages, odds ratios (OR), risk ratio's (RR) and hazard ratio's (HR), in accordance with study design and available data. When unavailable, RR's and OR's were calculated. All ratios were used to answer the main questions qualitatively. No quantitative analyses were conducted for this systematic review.
- Study registration: PROSPERO, CRD42021286193
- Patient and public involvement

Critical appraisal

Effect measures

- None
- Results
- Article selection

Our PubMed database search until November 2023 vielded a total of 25969 articles. After duplicate removal, 20,427 articles remained, that were screened for title and abstract. Following title and abstract screening, 172 articles were eligible for full text screening. All 172 articles could be retrieved. After full text screening, 48 studies were included for this review. Main reasons for exclusion were outcome that was not in our inclusion criteria, publication type, study design, population, and different drug. Article screening is summarized in the flowchart in Figure 1. 

Study characteristics 

Included studies, which are summarized in Tables 2-10, consisted of 21 cohort, 19 case-control and 8 pharmacovigilance studies. Drugs with reported Wnt activating properties included were VPA (13 studies), lithium (15 studies), haloperidol (7 studies), cimetidine (10 studies), clozapine (9 studies), and olanzapine (7 studies). Some studies assessed multiple drugs of interest. 

Studies were performed in multiple countries, including multiple European and Asian countries in addition to the USA. Additionally, a WHO pharmacovigilance database consisting of 160 countries was included (34). Most common indications were psychotropic, gastro-intestinal and neurologic use. All compounds were administered systemically in clinical dosing. Most studies assessed any type of cancer prevalence. All studies assessed cancer risk by analyzing clinical data or performing questionnaires. In addition, a few studies included histological verification for cancer diagnosis in addition to 

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- 159 clinical data (35–38). All Wnt activating compounds were used in their clinical dose 160 respective to their indication.
- <sup>6</sup> 161 *Risk of Bias*

Based on the Newcastle Ottawa Scale, all but one included study concerning VPA were determined to have a low risk of bias (Tables 11&12). One study by Stritzelberger et al.
 (Table 12) did not show all data concerning VPA (39).

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 13
 165 Concerning Lithium, for both cohort and case-control studies, most studies were
 166 determined to have low risk of bias (**Tables 13&14**). One cohort study by Zaidan et al.
 167 (**Table 13**) and three case-control studies by Hallas et al., Kahan et al. and Tamim et al.
 168 (**Table 14**) were subject to a high risk of bias (40–43).

18 169 Most studies reporting cimetidine use had a high risk of bias (Tables 15&16). Main points were missing data, lack of control group or no comparability of groups. The cohort study by Velicer et al. (Table 15) was determined to be of fair risk of bias (44). Only the study
 172 by Rossing et al. (Table 15) was determined to be of low risk of bias (44).

For haloperidol, both the cohort study by Wang et al. (Table 17) and the case-control study by Friedman et al. (Table 18) were determined to have low risk of bias (Wang et al. 2002, Friedman et al. 2020). The risk of bias in the case-control study by Hsieh et al. (Table 18), was high because they used non-gastric cancers as a control for gastric cancer instead of healthy individuals with no cancer (Hsieh et al. 2019). The case-control study by Pottengard et al. (Table 18) was determined to be of good quality (37). 

- 32 179 Outcomes
- <sup>33</sup> <sub>34</sub> 180

# 35 181 VPA

Seven cohort studies assessed the association between VPA use and cancer prevalence (35,45–50). 6 studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively [(46) RR = 0.877 (0.642 - 1.032);(47), RR=1.18 (0.96–1.46), (48), RR= 0.848 (0.563-1.277); (50) RR= 0.848 (0.563-1.277); (35), HR = 0.96 (0.84-1.19) 1.0 (0.8-1.3) 1.0 (0.7-1.3) (49), RR= 1 (0.7-1.3)]. The study by Chavez et al. evaluated melanoma prevalence in VPA exposed individuals. In this study, VPA exposed individuals had a significantly reduced prevalence of melanoma compared to controls [(51) HR = 0.64 (0.51-0.79)]. 

Additionally, 6 case-control studies assessed the association between VPA use and cancer prevalence (38,39,43,52-54). All studies showed no statistically significant increase in cancer prevalence between exposed versus controlled subjects respectively [(55), OR= 0.85, 0.70-1.04; (43), OR= 1.21 (0.95-1.56); (39), p=0,760; (52), OR= 0.62 (0.42-0.92); (38), 0.2% cases and 0.2% control group); (54), OR = 0.58 (0.39-0.56). 

54 195 Lithium

<sup>55</sup> 196 Nine cohort studies assessed the association between lithium use and cancer
 <sup>56</sup> 197 prevalence, including melanoma, urinary tract tumors, malignant neoplasms, invasive
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breast cancer and any type of cancer (42,48,49,55-60). Six studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively [(36) OR=1.19 (0.71-2.01); (57) RR= 1.01 (0.97-1.05); (60) Risk difference = -2.8% (-9.7-4.1) for cohort 1 compared to -3.0% (-6.0-0.1) for cohort 2; (58) RR=1.04 (0.89-1.23); (55) RR= 0.92 (0.58-1.46); (49) RR=1 (0.6-1.6)). Asgari et al. and Huang et al. evaluated cancer risk in lithium exposed individuals compared to controls. In both studies lithium exposed individuals had a significantly reduced cancer risk compared to controls [(56) unadjusted HR=0.68 (0.51-0.90); (48) RR= 0.426 (0.186-0.975)]. Zaidan et al., found an increased risk of renal tumors in patients exposed to over 20 years of lithium in comparison to both the general population and to kidney function matched controls (based on glomerular filtration rate) p=0.04 (42). 

Additionally, six case-control studies assessed the association between lithium use and cancer prevalence (40,41,43,54,61,62). five studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively ((41) 0.8% versus 0.9% incidence; (62) OR= 1.01 (0.86-1.19) for any use, OR= 1.06 (0.84-1.34) for >5 years use: (40) standardized incidence ratio= 0.93(0.6-1.38) for male subjects and 1.25 (0.91-1.69) for female subjects; (61) OR = 1.3 (0.7-2.1) Li et al. (2024), OR = 0.81 (0.58-1.12)). Hallas et al. (2009) showed a slight increase in cancer prevalence in subjects with long term exposure to lithium (43), OR = 1.19 (1.03-1.39)). 

#### Cimetidine

Three cohort studies assessed the association between cimetidine use and cancer prevalence (63-65). The study by Moller et al. did not include a control group (Moller et al. 1989). The remaining two cohort studies investigated gastrointestinal, breast and prostate cancer risk and found no significant increase in cancer risk in the groups exposed to cimetidine in comparison to controls (63) RR = 0.97 (0.61-1.53); (65) RR = 0.9 (0.8-1.1) for breast cancer risk in women and RR = 0.7 (0.6-0.8) for prostate cancer in men). Rossing et al. found a slightly increased risk of prostate cancer in a subgroup of men who had filled >21 prescriptions of cimetidine, (65), RR = 1.4 (1.0-1.9)). 

Five case-control studies assessed the association between cimetidine use and cancer prevalence (66-70). In all studies, cimetidine exposed individuals showed no significant difference in ratio compared to controls (66) OR=0.9 (0.6-1.2); (67), OR = 0.39 (0.17-0.89); (70) ductal carcinoma, ever use: OR= 1.1 (0.8-1.5); >2 years use, 0.9 (0.5-1.5); (69) (1992), no analysis reported; (68), (1990), OR= 2.1 (0.7-6.3)). Lastly, a cohort study and a surveillance study conducted by Colin Jones et al. showed no increased cancer prevalence after cimetidine exposure (71,72). 

Haloperidol

A cohort study by Wang et al. assessed the association between haloperidol use and breast cancer prevalence, including a total of 46,269 women. A breast cancer incidence of 0.052% (1228 cases in 237242 person-years in control group and 240 cases in 46269 person years in haloperidol group) was found in both exposed and unexposed groups, 

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<sup>3</sup> 238 indicating no significant increase in breast cancer incidence in women exposed to haloperidol compared to unexposed women (73).

Additionally, three case-control studies assessed the association between haloperidol use and cancer prevalence. A case-control study by Friedman et al. found a potential negative association between haloperidol use and prostate cancer risk, compared to controls depending on duration (74), at >2 years of use, OR = 0.54 (0.20-1.44), at >1 year of use OR = 0.32 (0.12-0.84), at <1 year of use, OR = 0.69 (0.48-0.99)). Another case-control study by Hsieh et al. found a reduced risk of gastric cancer associated with haloperidol use (75) OR = 0.25 (0.14-0.46)). A third, population-based case-control study by Chen et al. assessed the risk of endometrial cancer after exposure to haloperidol and other antipsychotics. For haloperidol, an increase of endometrial cancer after exposure to haloperidol was found (76) (OR= 1.75 (1.31-2.34)). 

Three database studies assessed the association between haloperidol use and cancer prevalence. The database study by Maeshima et al. using the Japanese adverse drug event database showed no increased risk of breast cancer in women exposed to haloperidol (77) ROR = 0.49 (0.07-3.51)). However, the study by Lertxundi et al. using the European pharmacovigilance database showed a possible increased risk of pituary tumors of subjects exposed to haloperidol (78), PRR= 7.0 (4.35-11.3)). Finally, a pharmacovigilance study using the adverse event reporting database from the U.S.A's food and drug administration by Szarfman et al. suggested a possible increased risk of pituary tumors in patients exposed to haloperidol (79) ARR= 5.6 (2.9-13)). 

<sup>31</sup> 259 Olanzapine

Three case-control studies assessed the association between olanzapine use and cancer prevalence. A nationwide case-control study by Pottengard et al. assessed the association between olanzapine use and breast cancer prevalence. Breast cancer cases were verified by histology. This study found a slightly increased risk of estrogen receptor-positive breast cancer in subjects exposed to olanzapine, attributed to its prolactin elevating properties when the study was only adjusted for age and gender(37) (aOR= 1.30; 95% CI = 1.09-1.56)); however, in the fully adjusted model, no significant increase was found (aOR= 1.15; 95% CI= 0.9-1.47). Another case-control study by Hsieh et al. found a reduced risk of gastric cancer associated with olanzapine use (75) OR= 0.13 (0.05-0.35)). Lastly, the case-control study by Chen et al. found no increased risk of endometrial cancer after exposure to olanzapine (80) (OR = 1.14 (0.56-2.30)). 

Three database studies assessed the association between olanzapine exposure and cancer prevalence (77–79). The database study by Maeshima et al. showed no increased risk of breast cancer in women exposed to olanzapine (Maeshima et al. (2021), ROR= 0.51 (0.07-3.51)). However, the database studies performed by Lertxundi et al. and Szarfman et al. suggested an increased risk of pituary tumors of subjects exposed to olanzapine (PRR= 2.53, (1.57-4.1) (78)); ARR=2.3 (1.4-3.7) (79)). 

<sup>3</sup>277

- Clozapine One cohort study by Tiihonen et al. assessed the risk of developing hematologic malignancies after exposure to clozapine. A significant, dose dependent, increased risk of hematologic malignancies was found (81) aOR= 3.35 (2.22-5.05) for >5000 defined daily dose cumulative exposure). Four case-control studies assessed the association between clozapine exposure and cancer prevalence. The case-control study by Hsieh et al. assessed the association between clozapine exposure and cancer prevalence and found a reduced risk of gastric cancer associated with clozapine use (Hsieh et al. (2019), OR = 0.35 (0.13-0.97)). The case-control study by Chen et al. found no increase in endometrial cancer risk after exposure to clozapine (80) OR = 1.14 (0.56-2.30)). The case-control study by Tilhonen et al. found an increased risk of hematologic malignancies after exposure to clozapine (81), aOR = 2.94 (2.07-4.17)). Interestingly, no significant difference for non-hematologic malignancies were found (81) for clozapine [aOR= 1.47 (1.25-1.47)]; as compared to other antipsychotics: [aOR=1.30 (1.15-1.47)]. Finally, the case-control study by Brainerd et al. also found an increased prevalence of hematologic malignancies after clozapine exposure in war veterans. OR = 1.31 (1.08-1.60) (82)
- Additionally, five database studies assessed the association between clozapine exposure and cancer prevalence. Two database studies by Szarfman et al. and Lertuxi et al., assessed the association of clozapine and pituary tumor prevalence. For clozapine, both studies showed no significant increase in pituary tumor prevalence in subjects exposed to clozapineARR= 0.9 (0.4-1.7) (79);PRR=0.98 (0.5-1.8) (78)). Two pharmacovigilance studies by Chrétien et al. and Dawson et al. assessed the risk of developing hematologic malignancies in subjects exposed to clozapine, due to the risk of severe haematologic side-effects when using clozapine. In the first study, clozapine exposed individuals had a significantly increased prevalence of leukemia aOR = 3.54 (2.97-4.22) and malignant lymphoma, aOR=9.13, (7.75-10.77) compared to controls) (34). In the second study an excess of hematologic malignancies in subjects exposed to clozapine was reported, indicating a possible increase in cases (no analysis performed) (83). Finally, a database study by Uwai et al. assessed the risk of non-hematologic malignancies in subjects exposed to clozapine. The study showed a possible relationship between clozapine and multiple non-hematologic malignancies including lung, gastrointestinal, esophageal, throat malignancies and metastases to the spine. (Uwai et al. (2024), Reporting odds ratio = 1.28 (1.22-1.34) (84)

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# <sup>3</sup><sub>4</sub> 310 Discussion

# <sup>5</sup> 311 Interpretation of the results/summary of main results

The aim of this review was to assess the risk of cancer development after the use of drugs that activate the Wnt pathway in humans. 48 observational studies (Tables 2-10) analyzing the risk of cancer of 6 different drugs that have known Wnt activating properties were included in this systematic review. The drugs assessed in this review were VPA, lithium, cimetidine, haloperidol, olanzapine, and clozapine. Most of the included studies showed no increase in cancer prevalence after being exposed to Wnt activating drugs. Most notably, are the 18 included cohort studies, which were assessed to have low risk of bias. These studies showed no increased cancer prevalence, and in some cases even a decreased cancer prevalence. These results suggest that using medication that activates the Wnt pathway in patients does not elevate cancer prevalence. 

A few included studies showed an increase in the prevalence of malignancies after usage of Wnt activating drugs. Interestingly, the included studies that showed an increase in cancer prevalence reported increased cancer prevalence for specific cancer types; there was not a systematic increase in cancer risk. The study by Zaidan et al., showed an increased risk of developing solid renal tumors after a median of 20 years of lithium exposure. However, as lithium is known to be nephrotoxic, and no systemic increase in cancer risk was observed, this increase in cancer prevalence could be attributed to direct toxicity, rather than the activation of the Wnt pathway (42). Chen et al. found an increased risk of endometrial cancer after exposure to haloperidol, attributed to antipsychotic-induced hyperprolactinemia, which is a common side-effect of antipsychotics, and not to the Wnt pathway activation. Of note are both olanzapine and clozapine, which also activate the Wnt pathway, but showed no increase in endometrial cancer risk (Chen et al. 2022). 

One study (which had many confounders and a high risk of bias), found an increased prevalence of gastric cancer in patients that had used cimetidine for gastric ulcers compared to the general population (72). No other included studies reported an increased cancer risk after cimetidine exposure. Therefore, it is not likely that cimetidine is carcinogenic. In this context, patients with gastric ulcers are already at a higher risk of developing gastric cancer (85). A better control for this study would have been patients with gastric ulcers and no cimetidine use. 

Lastly, and most notably, multiple studies found an increased prevalence of hematologic malignancies in subjects that were exposed to clozapine (Chrétien et al. 2021, Dawson et al. 2022, Tiihonen et al. 2023). Clozapine is well-known as the first second generation (atypical) antipsychotic and gold standard drug for treatment-refractory schizophrenia, but it has many adverse effects. Agranulocytosis is a relatively common and well-known side-effect of clozapine (86). Bone marrow toxicity has been described in *in vitro* studies (87). The pathogenesis of clozapine-induced agranulocytosis or bone marrow toxicity is still not clear; however, it is unlikely to be Wnt associated. Multiple alternative hypotheses 

have been described (86), all non-related to the Wnt pathway activation. In the case-control study performed by Tiihonen et al., they reported no differences in non-hematologic cancer risk for clozapine in comparison to other antipsychotic drugs (Tiihonen et al. 2022). Based on available data, we can conclude that subjects exposed to clozapine are at an increased risk of hematologic cancers, due to direct bone marrow damage, unrelated to its Wnt pathway activating properties. The fact that the increased cancer risk in patients exposed to clozapine has only been found in hematologic malignancies and not in solid tumors supports this hypothesis. 

In addition to cohort and case-control studies, multiple pharmacovigilance/surveillance studies were included in this systematic review (Tables 2-10). The pharmacovigilance/surveillance studies by Lertxundi et al. and Szarfman et al. showed an increased risk of developing pituary tumors after being exposed to the antipscyhotics haloperidol and olanzapine(78,79). Nonetheless, this risk was attributed to antipsychotic-induced hyperprolactinemia, which is a common side-effect of antipsychotics, and not to the Wnt pathway activation. None of the included studies showed an increased risk of non-pituary malignancies. Therefore, we can conclude the increase in cancer risk is not caused by the Wnt activating properties of these drugs. 

26 367 Strengths and weaknesses of the review

We assessed the cancer risk of multiple drugs with laboratory proven Wnt pathway activation. Most of the included drugs activate the Wnt pathway through GSK3-Beta inhibition (**Table 1**) (88,89). Since the activation of Wnt is not their main therapeutic target, the level of Wnt activation may differ between various drugs. However, to assess all data available on the prevalence of cancer after usage of drugs that activate Wht, we included all available mechanisms to Wnt activation. This study therefore included all papers available. 

- 37 375 This systematic review included a complete search of all data available until November
   38 376 1st, 2024. Moreover, bias was minimized by using two independent authors in the
   377 screening process.
- <sup>41</sup><sub>42</sub> 378 Strengths and weaknesses of the included studies

In this review, a total of 48 studies were included, summing up extensive data on multiple drugs activating the Wnt pathway. Notably, 21 cohort studies were included, of which 18 were assessed to be subject to a low risk of bias. This leads to an extensive dataset on the cancer risk of these compounds. Opposed to the cohort studies, however, the 19 included case control studies involved a wide variety in risk of bias and study methods. Notably the articles regarding cimetidine, which were relatively old overall, showed a high risk of bias. 

The wide variety in study designs, types of patients, cancer types and used compounds, resulting in heterogeneity in the data prevented us from conducting a meta-analysis, 388 which results in limitations in drawing an overall conclusion regarding the cancer risk of
 389 Wht pathway activation.

Another limitation is the drugs that were assessed in the included studies of this review. These drugs activate the Wnt pathway, but they are not specifically designed and used for their Wnt activating properties. These drugs have been in use since the 1950's and their Wnt activating properties have been described only in the last 30 years, mainly in in vitro experiments. Novel Wnt activating drugs, like CHIR99021 (90), have been produced in the past few years. However, given that these drugs have not been used clinically, their risk is not clear and has to be assessed in the future. Furthermore, included studies had considerable missing data, including data to assess dose-related cancer risk, such as duration of treatment and used dosages. In most articles, Wnt activating properties were not discussed. Finally, there were no randomized controlled trials included in this review; only observational studies were included which are by design more at risk of bias due to the lack of randomization.

# 22 402 **Conclusions**

As previously discussed, various applications are being researched for both activating and inhibiting the Wnt pathway. Cancer risk, however, remains a big concern (29). The results from this systematic review show that, at least for the compounds included in the currently used systemic dosage, no increase in cancer prevalence was found in any of the studies included, which could be attributed to Wnt pathway activation. These findings suggest that compounds activating the Wnt pathway are, regarding cancer risk a safe option. 

410 Before taking this conclusion into medical practice, however, further research on higher
 411 dosages, local administration and drugs specifically designed to induce Wnt activation
 412 should determine whether the activation of the Wnt pathway is indeed a safe treatment
 413 option with regards to cancer risk.

- In the regenerative therapy field, Wnt activation is a promising agent for future treatment
   opportunities. Based on the data in this review, we can conclude that Wnt activation by
   the assessed compounds leads to no increased cancer risk. Therefore, further research
- $\frac{41}{43}$  417 into Wnt activation as a treatment option should be explored.
- 45 418 **Statements**
- 46 419 Ethics approval
- <sup>48</sup><sub>49</sub> 420 No ethics approval was required for this study

Compound	Mechanism of action
Cimetidine	GSK3beta inhibition (88)
Clozapine	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin(91)
Haloperidol	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin(91)
Lithium	GSK3beta inhibition(88)
Olanzapine	GSK3beta inhibition(88)
'alproic acid	GSK3beta inhibition(88)

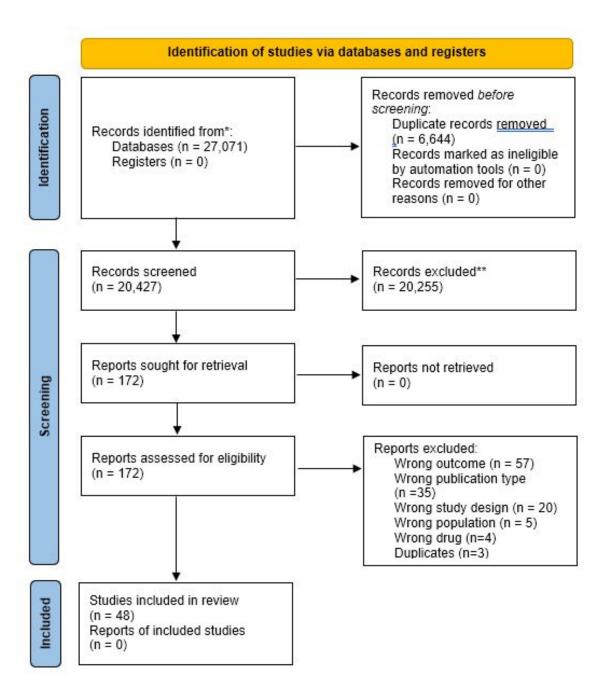


Figure 1: Article selection flow diagram. The identification of studies via databases and registers is presented above.
 The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion.
 The protocol was performed based on the PRISMA 2020 flow diagram for new systematic reviews which included
 searches of databases and registers only.

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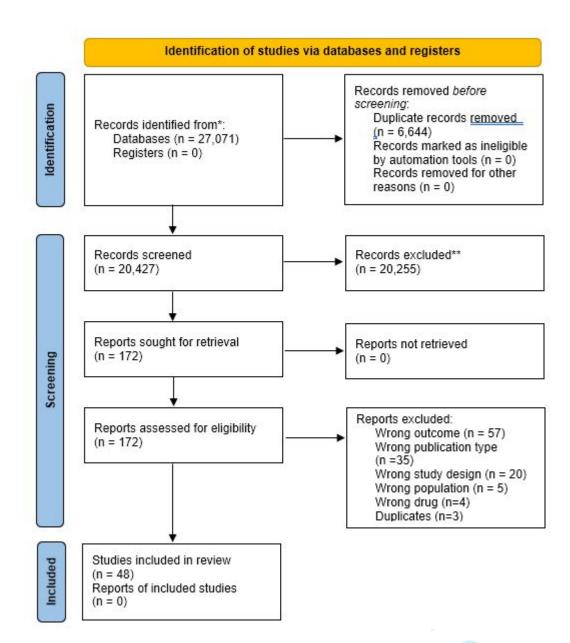
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38 39 40 41 42 43	671 672 673 674	77.	Maeshima T, Iijima R, Watanabe M, Yui S, Itagaki F. Effect of antipsychotics on breast tumors by analysis of the Japanese Adverse Drug Event Report database and cell-based experiments. J Pharm Health Care Sci [Internet]. 2021 Dec 1 [cited 2023 Nov 14];7(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33789764/
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50 51 52 53	679 680 681	79.	Szarfman A, Tonning JM, Levine JG, Doraiswamy PM. Atypical antipsychotics and pituitary tumors: a pharmacovigilance study. Pharmacotherapy [Internet]. 2006 Jun [cited 2023 Jul 2];26(6):748–58. Available from: https://pubmed.ncbi.nlm.nih.gov/16716128/
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3 4 5	684 685		Case-control Study. Clin Psychopharmacol Neurosci [Internet]. 2022 Aug 1 [cited 2024 Dec 2];20(3):526–35. Available from: https://pubmed.ncbi.nlm.nih.gov/35879037/	
6 7	686 687	81.	Tiihonen J, Tanskanen A, Bell JS, Dawson JL, Kataja V, Taipale H. Long-term treatment with clozapine and other antipsychotic drugs and the risk of haematological malignancies	
8 9	688		in people with schizophrenia: a nationwide case-control and cohort study in Finland.	
10	689		Lancet Psychiatry [Internet]. 2022 May 1 [cited 2024 Dec 2];9(5):353–62. Available	
11	690		from: https://pubmed.ncbi.nlm.nih.gov/35334224/	
12 13		~		
14	691	82.	Brainerd DR, Alexander B, Tague MJ, Lund BC. Association Between Clozapine	
15	692		Exposure and Risk of Hematologic Malignancies in Veterans With Schizophrenia. J Clin	
16 17	693		Psychiatry [Internet]. 2024 Jun 1 [cited 2024 Dec 2];85(2). Available from:	
17	694		https://pubmed.ncbi.nlm.nih.gov/38767931/	
19	695	83.	Dawson JL, Sluggett JK, Procter NG, Myles N, Bell JS. Hematological and Other Cancer	S
20	696		in People Using Clozapine: Analysis of Australian Spontaneous Reports Between 1995	
21 22	697		and 2020. J Clin Psychopharmacol [Internet]. 2023 Jul 1 [cited 2024 Dec 2];43(4):333-8.	
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26 27	700		Database. Drugs Real World Outcomes [Internet]. 2024 Jun 1 [cited 2024 Dec	1
28	701		2];11(2):185–93. Available from: https://link-springer-	
29	702		com.utrechtuniversity.idm.oclc.org/article/10.1007/s40801-024-00417-2	
30 21	105		com.utreentumversity.ium.oeie.org/article/10.1007/340801-024-00417-2	
31 32	704	85.	Søgaard KK, Farkas DK, Pedersen L, Lund JL, Thomsen RW, Sørensen HT. Long-term	
33	705		risk of gastrointestinal cancers in persons with gastric or duodenal ulcers. Cancer Med	
34	706		[Internet]. 2016 Jun 1 [cited 2023 Nov 15];5(6):1341. Available from:	
35 36	707		/pmc/articles/PMC4924392/	
30 37	708	86.	Legge SE, Walters JT. Genetics of clozapine-associated neutropenia: recent advances,	
38	709	00.	challenges and future perspective. https://doi.org/102217/pgs-2018-0188 [Internet]. 2019	
39	710		Feb 15 [cited 2023 Nov 15];20(4):279–90. Available from:	
40 41	711		https://www.futuremedicine.com/doi/10.2217/pgs-2018-0188	
41				
43	712	87.	Pereira A, Dean B. Clozapine bioactivation induces dose-dependent, drug-specific toxicit	y
44	713		of human bone marrow stromal cells: A potential in vitro system for the study of	
45 46	714		agranulocytosis. Biochem Pharmacol. 2006 Sep 14;72(6):783-93.	
47	715	88.	Furuta T, Sabit H, Dong Y, Miyashita K, Kinoshita M, Uchiyama N, et al. Biological	
48	716	55.	basis and clinical study of glycogen synthase kinase- $3\beta$ -targeted therapy by drug	
49 50	717		repositioning for glioblastoma. Oncotarget [Internet]. 2017 Feb 9 [cited 2023 Nov	
50 51	718		15];8(14):22811–24. Available from: https://www.oncotarget.com/article/15206/text/	
52				
53	719	89.	Sutton LP, Honardoust D, Mouyal J, Rajakumar N, Rushlow WJ. Activation of the	
54	720		canonical Wnt pathway by the antipsychotics haloperidol and clozapine involves	
55 56	721		dishevelled-3. J Neurochem. 2007 Jul;102(1):153–69.	
57				
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59			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	3
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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 9 20 21 22 32 4 25 26 27 28 29 30 31 32 33 4	722 723 724 725 726 727 728 729 730 731	90. 91.	<ul> <li>Yoshida Y, Soma T, Matsuzaki T, Kishimoto J. Wnt activator CHIR99021-stimulated human dermal papilla spheroids contribute to hair follicle formation and production of reconstituted follicle-enriched human skin. Biochem Biophys Res Commun [Internet]. 2019 Aug 27 [cited 2021 Dec 3];516(3):599–605. Available from: https://pubmed.ncbi.nlm.nih.gov/31221480/</li> <li>Sutton LP, Honardoust D, Mouyal J, Rajakumar N, Rushlow WJ. Activation of the canonical Wnt pathway by the antipsychotics haloperidol and clozapine involves dishevelled-3. J Neurochem [Internet]. 2007 Jul [cited 2021 Nov 30];102(1):153–69. Available from: https://pubmed.ncbi.nlm.nih.gov/17472703/</li> </ul>
33			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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A	ppendix: Compounds in search string.
A	R-A014418
A	ZD-1080
С	chir-99021
С	HIR98014
С	limetidine
F	X-322
G	Semifloxacin
Η	lydroxychloroquine
Li	ithium
Ľ	Y2090314
0	Dianzapine
S	B216763
ΤI	DZD8
Ti	ideglusib
T	WS119
T	WS119
V	alproic acid



**Figure 1:** Article selection flow diagram. The identification of studies via databases and registers is presented above. The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion. The protocol was perfomed based on the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

#### Table 11. Critical appraisal table for cohort studies on the use of VPA

titveness of cohort         Selection of non- exposed cohort         Ascertainment of exposure         outcome of non- study         Ascertainment of exposure         outcome of more study         Ascertainment of exposure         Max 2 strat of study         Ascertainment of outcome         outcome of more study         Ascertainment of exposure         Max 2 strat of study         Ascertainment of outcome         Ascertainment of exposure         Ascertainment study         As	able 11. C	ritical a	ppraisal table fo	or cohort studi	es on the use of VPA	BM.	J Open	/bmjopen-20 d by copyrig			F	Page 28 of 6
titveness of cohort         Selection of non- exposed cohort         Ascertainment of exposure         outcome of interest was not present at start of study         Max 2 strat of refuse to the study         Ascertainment of outcome of interest was not present at start of study         Max 2 strat of refuse to the study         Ascertainment of outcome of interest was not present at start of study         Ascertainment of outcome         Assertainment of outcome								ht, includin	(n			
on June 8, 2025 at Agence milar technologies.	Author	Year	Type of study	titveness of			outcome of interest was not present at start of	of cohorts a (max 2 son	Ascertainment of outcome	enough	of follow	Verdict
on June 8, 2025 at Agence milar technologies.	Chavez	2020			*	*	*	9025. D gneme elated *	*	*		Good
on June 8, 2025 at Agence milar technologies.	Lin	2018	cohort study	*	*	*	*	ownlo ent Sul *	*	*		Good
on June 8, 2025 at Agence milar technologies.	Huang	2016	cohort study	*	*	*	*	aded ↑ perieu * d c *	*	*	*	Good
on June 8, 2025 at Agence milar technologies.	Каае	2010	based cohort	*	*	*	*	from http r (ABES lata min *	*	*	*	Good
on June 8, 2025 at Agence milar technologies.	Kang	2014			*	*	*	) ing, A ** A	*	*	*	Good
on June 8, 2025 at Agence milar technologies.	Singh	2011	cohort study	*	*	*	*	jopen.bm I training, *	*	*	*	Good
on June 8, 2025 at Agence milar technologies.	Yang	2022		*	*	*		and si *	*	*	*	Good
ographi ique de								Agence Bibliographique				

5	29 of 60 Ible 12. Critical	appraisa	al table for case c	ontrol studies on t	he use of V:		MJ Open	rability	/bmjopen-2025			
1 2					Selection (max 1 sta	ı	Compare (max 2	rability ngnt, stars) ,	1-2025-10	(		
3 4 5 6 7 8	Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases		Definition of controls	Comparability do cases and controls	FF 36 Ma En:	certain nent of utcome	Non- response rate	Verdict
9 10	George	2023	case-control	*	*	*	*	**	2025 Pigne	*	*	Good
11 12	Hallas	2009	case control	*	*	*	*	** to	. Dov	*	*	Good
13 14	Li	2024	Nested Case control	*	*	*	*	** Xta	y 2025. Downloaded fro seignement Superieur (	*	*	Good
15 16	Kristensen	2019	nested case control	*	*	*	*	ha data	led froi rieur (/	*	*	Good
17 18	Salminen	2016	case-control	*	*	*	*	** 11		*	*	Good
19 20	Stritzelberger	2020	Nested case control	N/A High ri	isk of bias, no	ot the aim of the	e study and not all data sho	own A				Poor
21 22	Tilhonen	2022	case-control	*	*	*	*	** tra	jope	*	*	Good
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41							- Charles	Al training, and similar technologies.	n.bmj.com/ on June 8, 2025 at Agence Bibliographique de l			
42 43				For pe	er review on	nlv - http://bmio	pen.bmj.com/site/about/g	auidelines.xhtml	de I			

					Selection nax 1 star)		d by copyright, includ	/bmjopen-2025-103296	Outcome (max 1 sta		
Author	Year	Type of study	Representatitveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparibility Q្ឆិ cohorts ថ្ (max 2 stars) ្អ ខ្លួំ ក្លួ	Ascertain Ment of Outcome	Long enough follow up	Adequace of follow up	Verdict
Asgari	2017	retrospectiv e cohort		*	*	*	tement s ++++++++++++++++++++++++++++++++++++	5. Down	*	*	Good
Lin	2018	retrospectiv e cohort study	*	*	*	*	ext and d *	* *	*		Good
Cohen	1998	,	*	*	*	*	data n **	from *	*	*	Good
George	2019	restrospectiv e cohort study	*	*	*	*	nining, Al	* http://bmj	*		Good
Huang	2016	retrospectiv e cohort study	*	*	*	*	l training, a *	; * jopen.bmj	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	eignement Superieur (ABES) . related to text and data mining, Al training, and similar technologies. * * * * * * * * * * * * * * * * * *	* *	*		Good
Kessing	2024	Cohort (Population based)	*	*	*	*	ar technolo *		*	*	Good
Martinsson	2016	Cohort nationwide		*	*	*		* 2025 at Aç	*	*	Good
Zaidan	2014	retrospective cohort study		ort compar <sup>,</sup>	ed to general po	opulation, expressed as		genceence ration	o; small cohor	t	Poor

AuthorYearType of studyRepresent Adequacy of case definitionSelection of controlsDefinition of controlsComparability cases and controlsNon- response rateNon- response rateVerHallas2009case control****Pointer of controlsNon- response rateVerKahan2018Case-control study from large database****Pointer of controlsNon- response ratePointer of controlsLi2024Nested Case*******Pointer of controls	AuthorYearType of studyAdequacy of case definitionRepresent ativeness of the casesSelection of controlsDefinition of controlsComparability cases and controlsNon- responseVerdic responseHallas2009case control*****PoorKahan2018Study from large databaseData from large database, scale non-applicable, high risk of bia rate****PoorLi2024Nationwide control**********PoorPottengard2016 (1)Nationwide study** <t< th=""><th></th><th></th><th></th><th></th><th></th><th>Selection (max 1 star) omparability</th><th></th><th>Comparability (Max 2 stars)</th><th>for</th><th>ຊີ (max 1 s</th><th></th><th></th></t<>						Selection (max 1 star) omparability		Comparability (Max 2 stars)	for	ຊີ (max 1 s		
Hallas       2009       case control       *	Tamim       2008       Nested case-       *       *       *       Poor         Study       5 <td< th=""><th>Author</th><th>Year</th><th>Type of study</th><th></th><th>ativeness</th><th>Selection of</th><th></th><th>cases and</th><th>mayqeoes Enseign usestgelat</th><th>scertain</th><th>response</th><th>Verdic</th></td<>	Author	Year	Type of study		ativeness	Selection of		cases and	mayqeoes Enseign usestgelat	scertain	response	Verdic
Kahan       2018       Case-control study from large database       Data from large database, scale non-applicable, high risk of bight for large database       Mester for angle database       Mester for angl	Tamim       2008       Nested case-       *       *       *       Poor         Study       5 <td< td=""><td>Hallas</td><td>2009</td><td>case control</td><td>*</td><td>*</td><td></td><td>*</td><td></td><td>Super</td><td>*</td><td>*</td><td>Poor</td></td<>	Hallas	2009	case control	*	*		*		Super	*	*	Poor
Li2024Nested Case control**********GoPottengard2016 (1)Case control study***<	Tamim       2008       Nested case-       *       *       *       Poor         Study       5 <td< td=""><td>Kahan</td><td>2018</td><td>study from</td><td></td><td>Dat</td><td>a from large dat</td><td>abase, scale non-applicab</td><td>le, high risk of bi</td><td>ieur (ABE</td><td>from</td><td></td><td>Poor</td></td<>	Kahan	2018	study from		Dat	a from large dat	abase, scale non-applicab	le, high risk of bi	ieur (ABE	from		Poor
Nationwide       Nationwide       *	Tamim       2008       Nested case-       *       *       *       Poor         Study       5 <td< td=""><td>Li</td><td>2024</td><td></td><td>*</td><td>*</td><td>*</td><td>*</td><td>**</td><td>≣S). ining, ∕</td><td>*</td><td>*</td><td>Good</td></td<>	Li	2024		*	*	*	*	**	≣S). ining, ∕	*	*	Good
Case control Pottengard 2016 (2) study * * * * * * * * * <mark>2 6 * * * Gonationwide study and study</mark>	Tamim       2008       Nested case-       *       *       *       Poor         Study       5 <td< td=""><td>Pottengard</td><td>2016 (1)</td><td>case control</td><td>*</td><td>*</td><td>*</td><td>*</td><td>**</td><td>N trainin</td><td>*</td><td>*</td><td>Poor</td></td<>	Pottengard	2016 (1)	case control	*	*	*	*	**	N trainin	*	*	Poor
	Tamim       2008       Nested case-       *       *       *       Poor         Study       5 <td< td=""><td>Pottengard</td><td>2016 (2)</td><td>study</td><td>*</td><td>*</td><td>*</td><td>*</td><td>**</td><td>g, and si</td><td>*</td><td>*</td><td>Good</td></td<>	Pottengard	2016 (2)	study	*	*	*	*	**	g, and si	*	*	Good
Lithium not make case- Tamim 2008 control * * * * * question of the study of the s	2025 at Agen	Tamim	2008	Nested case-	*				Lithium not ma question of study	mi <u>t</u> ar techr	-	*	Poor

							ыу сорунунын,	+ N			
				Selecti	on (max 1 star)		-	/bmjopen-2025-103296	Dutcome (max	1 star)	_
Author	Year	Type of study	Representatitvenes s of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability cohorts (max 2 stars)	Ascertain Scent of	Long enough follow up	Adequace of follow up	Verdi
Moller	1989	Cohort	No control, high risk o	of bias				25. Dov			Роо
Rossing	2000	Retrospective cohort study	*	*		*	**	* * t Super	*	*	Good
Velicer	2006	Cohort study		*		*	** 0	ieur *	*	*	Fair
						*		with the second of the second			
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					Selection (max 1 star)		Comparibility (Max 2 stars)	)은 C (max	tcome ( 1 star)	
Author	Year	Type of study	Adequacy of case definition	of the	Selection of controls	Definition of controls	Comparability cases and controls	Generation Genera	n Non- f response e rate	Verdic
Colin Jones	1985	case control study	No representativ	e outcome;	already had gas	trcic ulcers, only age and s	sex matched con	5. Dov em@nt ted∯o		Poor
Colin Jones	1991	surveillance study	No control, N/A			trcic ulcers, only age and s		vnload Supe text a		N/A
Coogan	2005	Database study/case- control	*		*		**	led from rieur (AB nd data n		Poor
Holly	1997	population- based case- control study				*	**	* http://bm ES) . ining, A		Poor
Mathes	2008	Population based case- control study	*	*	*	*	**	* jopen.bn I training		Good
Moller	1992	Case-control study	High risk of bias	;				* * from http://bmjopen.bmj.com/ on June 8, ur (ABES) . data mining, Al training, and similar techn		Poor
Schumacher	1990	Case-control study	*	*			**	June 8, 2025 at . ar technologies.		Poor
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					Selection (max 1 star)		Vbmjopen-2025-103296 gn d by copyright, includin <b>ili</b> d by copyright, includin <b>ili</b>	(n	Dutcome nax 1 star)	
Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	- Comparibility of cohogts a (max 2 s∰ars) es saves aves aves aves aves aves aves aves	Ascertainment of outcome	Long enough follow up	Adequa of follo up
Tilhonen	2022	cohort study	*	*	*		2025. elate *	*	*	
Wang	2002	Retrospective cohort	*		*	*	5. Downloaded fro ament Superieur ( ed to text and dat *	*	*	*
						**	loaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique uperieur (ABES) . xt and data mining, Al training, and similar technologies.			
				For peer review	only - http://bmjope	n.bmj.com/site/about/guide	de			

Verdict

Good

Good

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				Selectio (max 1 st		Comparibili (max 2 star	5 0	ภิ	Outcome (max 1 star)		
Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	Comparibility		certain	Non- response rate	Verdic
Brainerd	2024	Case Control study	*	*	*	*	**	nent Su d to tex	Downlo	*	Good
Chen	2022	Case-control study	*	*	*	*	**	perieur t and d	* *	*	Good
Friedman	2020	Case-control	*	*	*	*	**	(ABES ata min	* *	*	Good
Hsieh	2005	Database study/case- control		Sc	ale not fully app	licable due to study desig	n, high risk of bia	) . ing, Al tra	o-//hmion		Poor; N,
Pottengard	1997	population- based case- control study	*	*	*	licable due to study desig	**	aining, ar	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	nd similar	*	*	Good
								technologies.	Boutcome * * * * * * * * * * * * * * * *		

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Table 2. Data extraction and results table for cohort studies on the use of VPA

Indication for

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	in Andralysis (95%) Luci 29	cancer prevalence	bias verdict
Chavez	2020	USA	Psychiatric	kaiser permanente consortium	92.6 per 100.000 person years	64 per 100.000 person years	including for R = 0.64 (0.51-0.79) Have a seignement Super seignement Super seignement Super seignement Super seignement and sei fr	No, decreased risk	Good
Lin	2018	Taiwan	Bipolar disorder	patients treated with anticonvulsants who did not use VPA	76/2663 (2.9%)	66/2663 (2.5%)	related to tr	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	ext and 88 (0.563-1.277) data data	No	Good
Каае	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any ECC 1.3(1.1-1.4), CMM 1(0.8 9) MCC 1.2(0.2-8.7), SCC 9 3.3(1.1-1.6) Per 5 eas of use: BCC 1.1 (0.9- 1.4); MM 1 0.9 (0.5-1.5) MCC Ne data; SCC 0.8 (0.5-1.4)	No dose response	Good
Kang	2014	USA	Phsychiatric or neurologic disease	Smokers, never used VPA	9957/412717 (2.41%)	491/26911(2.58%)	السام (2013) lung (2019) prostage (6,97), colon and rectum (0.93), bladder (0.93)	No	Good
Singh	2011	UK	Neurologic	Unexposed to VPA	4.56 (4.19–4.96) /1000 person years n= 551	5.11 (4.37–5.98)/1000 person years n=155	Rate rates g. 25 e. 21 Rate rates g. 25 e. 21 Rate rates g. 25 e. 21 Rate rates g. 25 e. 21 Rate rates g. 25 e. 25	No	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.887 (0.642-1.032)	No	Good
				For peer review onl	y - http://bmjopen.br	nj.com/site/about/guideline	Bibliographique de l es.xhtml		

**Risk of** 

Increase in

5	e 37 of 60 Table 3. Data extr	raction and	l results table	for non-cohort	studies on the use	BMJ Op e of VPA	ben	/bmjopen-2025-103 4 by copyright, inclusiin		
3 4	Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (25%)	Increase in cancer prevalence	Risk of bias verdict
5 6 7 8 9	George	2023	Sweden	Antiepileptic	Matched controls	766 without cancer and exposed to VPA / 156036	117 patients with cancer exposed to VPA /31474	ng for (95% (86) 0.85 OR (95% (86) 0.85 (0.888 0.100) Srational (0.888 0.100) Srational (0.888 0.100) Srational (0.85) Srational (0.85) Srati	no	Good
10 11 12 13 14	Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	related at Suppose OR = 1.56) OR = 1.56) text a	No	Good
15 16 17 18 19	Li	2024	Taiwan	Psychiatric	Matched controls	15540 matched controls	33 cases exposed (8.1%) 1438 cases unexposed (9.1%)	and date from 9-0.56) OR=0.58 minin	Decrease	Good
20 21 22	Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	1623 (0.2%)	162 (0.2%)	No significant difference R not reported	No	Good
23 24	Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	Х	X	0.62 (@42-992) OR	Decrease	Good
25 26 27	Stritzelberger	2020	Germany	Neurologic	Epilepsy without cancer	21.0% of non cancer cases used VPA	21.5% of cancer cases used VPA	and sumilar	No	Poor
28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46				Fo	r peer review only -	http://bmjopen.br	mj.com/site/about/guidelin	ne 8, 2025 at Agence Bibliographique de technologies.		

						d by copyright, i	2025-		
Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt n group = u prevalence g	/bmjopen-2025-103296 c	Increase in cancer prevalence	Risk of bias v
Asgari	2017	USA	Ever exposed	Kaiser permanente consortium	14008 (92.5 per 100,000 person years)	48 (67.4 per 9 100,000 person 5 r years) 8 r	₹anadjusted = 0.68 <b>€</b> 0.51-0.90); HR ■ djusted: 0.77 ■ (0.50.402)	No, decrease	Good
Lin	2018	Taiwan	Bipolar disorder	Patients treated with anticonvulsants who did not use lithuim	48/1850 (2.6%)	26/925 (2.8%) to text a		No	Good
Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	19/609 (3.12%) a figur 19/609 (3.12%)		No	Good.
George	2019	USA	Antiphysicotic medication	Postmenopausal women not treated with lithium	10079/155095 (6.5%)	лд, . 18/326 (5.5%) А trai	0.58-1.46)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	بة 0 patients (1.6%) ه	26 (0.186-0.975)	No, decrease	Good
Kessing	2015	Denmark	Psychiatric	Randomly selected sample from Danish population	Total amount of subjects: 24.272	(0.86%) ar	end test: HR = 1.01 (0.97-1.05)	No	Good
Kessing	2024	Denmark	Psychiatric	Lamotrigine use	Cohort 1: 4,281 (18.7%) Cohort 2: 71,069 (21.4%)	Cohort 1: 4,496 (15.8%) Cohort 2: 13,422 (18.3%)	Risk difference= Cohort 1: -2.8% (- S 9.7%; 4.1%) Ghort 2: -3.0% (- A 6.0%; -0.1%)	No	Good
Martinsson	2016	Sweden	Psychiatric	General population compared to Bipolar disorder (with and without lithium)	166,443 (6.4%)	142 (5,9%)	Gence 04 (0.89-1.23)	No	Good
Zaidan	2014	France	Bipolar disorder	Matched (EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	ograp p=0.04	Yes	Poor

44 45 46

Table 5. Data extraction and results table for case-control studies on the use of lithiun	า
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alysis (95 conversion of the second s
9 (1.03-1.39) 8 shown, not the main andardize
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5 (0.91-1.69) 🛱 🎽
5 (0.91-1.60)X Superied = 0.81 (0.53) (A BES) (0.91-1.60)X Superied = 0.81 (0.53) (A BES) (0.91-1.60)X Superied No Good
1(0.86-1.1 <b>2</b> ) Solution Solution
= 1.3 (0.7-41) No Good
b significant difference differen
on June 8, 2025 at Agence Bibliographique milar technologies.
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1	Table 6. Da	ata extract	ion and result	s table for cohc	ort studies on the	e use of cimetidine	BMJ Open		in /bmjopen-2028 /bmjopen-2028 /by copyright, in		
2 3 4	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	ht, Increase in Increase in Compression Concer	Exposure duration	Risk of bias verdict
5 6	Moller	1989	Denmark	Gastro- intestinal	No control, na	tional incidence		RR= 1.5 (p<0.001)	ing for L	not specified	Poor
7 8 9 10	Rossing	2000	USA, western Washington State	Gastro- intestinal	All males/females in the area	Total cohort = 48.512 users. Cases not shown	267 cimetidine Cases	0.9 (0.8–1.1)	0 May <sup>2</sup> 025. Enseigner uses relate	not specified	Good, however not all data shown.
11 12 13 14 15	Velicer	2006	USA	Gastro- intestinal	Victims and lifestyle cohort	478 (1.8%) (incidence=7.6)	20 (1.6%)(incidence is 8.5)	RR= 0.97 (0.61- 1.53)	Dowfiloade nent Superi d to text an	not specified	Fair
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 22 33 34 35 36 37 38 39 40 41 42 43 44							open.bmj.com/site/ak		, 2025 at Agence Bibliographique de nologies.		

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#### BMJ Open

of 60 le 7. Data extra	action and resu	ilts table	e for surveil	lance and ca	ase-control s	BMJ Open studies for the use		/bmjopen-2025-1032段 o J by copyright, including		
Type of study	Study	Year	Location	Indication for use	Control condition	Controls	Cases	cluding for on	Increase in cancer prevalence	Risk o bias verdio
Surveillance	Colin jones	1991	UK	Gastro- intestinal	x	x	111/9928 (1.1%)	or 3 u NO control group!	No	Poor
Surveinance	Colin jones	1985	UK	Gastro- intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	REAL Secontrol group! Secontrol group! Secontrol group! Secontrol group! Secontrol group! Secontrol group! Secontrol group! Secontrol group!	No	N/A
	Coogan	2005	USA	Gastro- intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	<b>6 9 0 1 1 1 1 1 1 1 1 1 1</b>	No	Роог
Case-control	Holly	1997	USA	Gastro- intestinal	Never use	x	x	text text Supperiod and ded dated from dated dated from	Decrease	Poo
	Mathes	2008	USA	Gastro- intestinal	Never users	n= 1390, 1136 (92.5%) unexposed; 92 5(7.5%) ever use; 36 (2.9%) > 2 years	Ductal carcinoma: n=1148; 939 (92.1%) never use; 81 (7.9%) ever use; 27 (2.6%)>2 years of use	Ever use Ever use 1.5); Logula carcinoma OR = 1.1 (0.8- 1.5); Logula carcinoma OR = 1.0 (0.7- 1.6); >2 pearsuse ductal carcinoma, 0.9 (0.5-1.5) tobe ar carcinoma, 1.1(0.6-1.9)	No	Goo
	Moller	1992	Denmark	Gastro- intestinal		l controls Group tional pharmacy	<u>(</u> 0),	$\vec{p}$ , $\vec{p}$	No	Роо
	Schumacher	1990	USA	gastro- intestinal	Non users	x	x	$O_{\underline{B}} = 2.1 (0.7 - 0.3)$ $O_{\underline{B}} = 2.21 (95\% \text{ Cl} = 0.7 - 6.3)$	No	Рос
								on June 8, 2025 at Agence Bibliographique de I milar technologies.		

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т	able 8. Data	a extraction ar	nd results tal	ble for cohort stu	udies on the use c		Open ozapine, and olanzapin	right,		
	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (35%)	Increase in cancer	Risk of bias verdict
	Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	ר אר	No	Good
	Tiihonen	2022	Finland	Clozapine (schizophrenia)	matched controls (schizophrenia patient without cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted O (2.22-5.05) >5000 define da dose cumulation exposure a	y Yes, hematologic	Good
							Prien	d data mining d data mining		
								ES) . ES) . nining, Al training, and similar technologies.		
								and similar t		
								chnologies		
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								gence provografindate de r		
				Fo	or peer review only	- http://bmjoper	.bmj.com/site/about/gui	idelines.xhtml	-	

### BMJ Open

	e 43 of 60					BMJ (		/bmjope 1 by cop		
1 2 3	Study	Year	Location	Drug of interest	Control Control condition	Controls	dol, clozapine, and olar Cases	Jbmjopen-2025 J by copyright, 1953 Analysis Cludir	Increase in cancer prevalence	Risk of bias verdict
4 5 6	Brainerd	2024	USA	Clozapine	Matched controls	23,043 (4.1%)	2,306(5.3%)	OR = 1.31 (1008-4.60)	Yes	Good
6 7 8				Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% CD is 875 (1.31-837)	yes	
8 9 10	Chen	2022	Taiwan	Olanzapine	Matched controls	63/37908	13/9502	OR (95% (1)) 22 (0.38-	no	Good
10 11 12			_	Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% 2) 34 (0.56-23) 2	no	
13 14					Not treated with	39553/1962602 (2.0%)	4/352 (1.1%)	OR = 0.54 (0228-0.44)	No	
15 16	Friedman	2020	USA	Haloperidol	haloperidol	576	4/576 (0.7%)	OR = 0.32 (0910 - 60.84)		Good
17 18				Clozapine	Non-gastric	2008	30/2008 (1.5%) 4 (0.01%)	OR = 0.69 (0 4 5 9.99) OR = 0.35 (6 1 7 1.97) OR = 0.35 (6 1 7 1.97)		
19 20	Hsieh	2019	Taiwan	Haloperidol	cancer Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (014-9.46)		N/A
21 22			-	Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (005 2).35)	No, decrease	
23 24 25 26 27	Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted Og 1:1:30 (1.09-1556) Adjusted Og 2: 1:15 (0.9-1 37) 2	No in fully adjusted model (2), yes when only adjusted for age and gender	Good
28 29 30 31	Tiihonen	2022	Finland	Clozapine	No cancer	3734 matched controls (9.9used clozapine%)	375 cases; 19,5% used clozapine.	(0.9-1477) - J ar technorod une aOR = 2.94 (307-84.17) es. at A	Yes, hematologic cancers	Good
32 33 34 35 36 37 38 39 40 41 42 43 44 45					For peer review o	only - http://bmjopen.	bmj.com/site/about/gui	gence Bibliographique de		

BMJ Open Table 10. Data extraction and results table for pharmacovigilance and database studies on the use of haloperidol, clozapine and objective and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol, clozapine and batabase studies on the use of haloperidol and batabase s

Study	Year	Drug of interest	Control condition	Type of cancer	Cancer risk Wnt group = prevalence	rright, includ	Increase in cancer prevalence	Risk of bia verdict
		Clozapine	х	Pituary tumor	17 cases	<b>a</b> RR 0.98 (0.5-1.8)	No	
Lertxundi	2019	Haloperidol	х	Pituary tumor	11 cases	₫RR = 7.0(4.35-11.3)	Possibly	N/A
		Olanzapine	х	Pituary tumor	17 cases	<b>5Rh≥</b> 2.53 (1.57-4.1)	Possibly	
		Clozapine	x	Pituary tumor	4 cases	24 t = 0.9 (0.4-1.7)	No	
Szarfman	2006	Haloperidol	х	Pituary tumor	9 cases	a A R = 5.6 (2.9-13)	Possibly	N/A
	-	Olanzapine	x	Pituary tumor	11 cases	2.3 (1.4-3.7)	Possibly	
		Clozapine	x	Hematologic malignancies	275	aR <b>Q</b> K 59.14 (7.75-10.77)	Possibly	
Chretien	2021	Olanzapine	x	Hematologic malignancies	68	aR05 30.88 (0.66- 1.16)	No	N/A
Maashima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1 0 0 0 0.07, 3.51) ROR	No	NI / A
Maeshima	2021	Olanzapine	x	Benign and malignant breast cancer	1825	239.501 239.501 10.07, 3.51) ROR	No	N/A
Dawson	2023	Clozapine	x	Hematological	104/384	excess of fine matological cancers in people exposed to clozapine	Possibly	
				Neoplasm	61/384	l tra	No	
				Lung	50*384	ini en.t	No	
				Breast	37/384	bmj.com/ ng, and si	No	
				Colorectal	28/384	and Cor	No	
				Brain	18/384	simil	No	
				Skin	17/384	open.bmj.com/ on June 8, 2025 at training, and similar technologies	No	NI / A
				Esophagogastric	11/384	June ar tec	No	N/A
				Pancreatic	10/384	8, N	No	
				Urological	9/384	2025	No	
				Testicular	8/384	jies	No	
				Hepatic	7/384		No	
				ENT	6/384	Agence	No	
				Gynecological	<5/384	e Bib	No	
				others	14/384	iblio	No	
Uwai	2024	Clozapine	х	All non-hematologic malignancies	1668	Reporti <b>स्ट्र</b> Odds Ratio= 1.28 द् <u>र</u> 1.22-1.34)	Possibly	N/A

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Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Vbmjopen-2025-1alysis (95%) by copyright, including fo R 유민이 (0.51-0.79)	Increase in cancer prevalence	Risk of bias verdict
Chavez	2020	USA	Psychiatric	kaiser permanente consortium	92.6 per 100.000 person years	64 per 100.000 person years	use use	No, decreased risk	Good
Lin	2018	Taiwan	Bipolar disorder	patients treated with anticonvulsants who did not use VPA	76/2663 (2.9%)	66/2663 (2.5%)	s related to text and c	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	ext and Super Bur (0.563-1.277) data	No	Good
Каае	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any ﷺ ∰ 5CC 1.3(1.1-1.4), CMM 1(0.8 ∰ 9 ∰ MCC 1.2(0.2-8.7), SCC 9 ⊕ 1.3(1.1-1.6) Per 5 ≩eas of use: BCC 1.1 (0.9- 1.4); ∰ M 1 0.9 (0.5-1.5) MCC Nadata; SCC 0.8 (0.5-1.4)	No dose response	Good
Kang	2014	USA	Phsychiatric or neurologic disease	Smokers, never used VPA	9957/412717 (2.41%)	491/26911(2.58%)	ي مجمع العلم المعام المعام معام المعام الم معام المعام المع معام المعام المع معام م معام الم	No	Good
Singh	2011	UK	Neurologic	Unexposed to VPA	4.56 (4.19–4.96) /1000 person years n= 551	5.11 (4.37–5.98)/1000 person years n=155	Rate rates at A	No	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.8 <b>6</b> 7 (0.642-1.032)	No	Good

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able 3. Data extr	action and	l results table	e for non-cohort	studies on the use	BMJ Op e of VPA	oen	/bmjopen-2025-10: 1 by copyright, incl		Page 46 of 6
Study	Year	Location	Indication for use	Control condition	Controls	Cases	Anatesis 25%)	Increase in cancer prevalence	Risk of bias verdict
George	2023	Sweden	Antiepileptic	Matched controls	766 without cancer and exposed to VPA / 156036	117 patients with cancer exposed to VPA /31474	ug fon OR (95% ይ) 0.85 (0.500 - 500	no	Good
Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	OR = 1.50 OR = 1.50 OR = 1.50 The second	No	Good
Li	2024	Taiwan	Psychiatric	Matched controls	15540 matched controls	33 cases exposed (8.1%) 1438 cases unexposed (9.1%)	and date OR=0.56) OR=0.56 minin	Decrease	Good
Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	1623 (0.2%)	162 (0.2%)	No significant difference R not reported	No	Good
Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	Х	X	0.62 (@42-992) OR	Decrease	Good
Stritzelberger	2020	Germany	Neurologic	Epilepsy without cancer	21.0% of non cancer cases used VPA	21.5% of cancer cases used VPA	and <u>st</u> mil	No	Poor
			Fc	or peer review only -	http://bmjopen.b	mj.com/site/about/guidelii	pimilar technologies.		

-	e 47 of 60 Table 4 Data ex	traction	and results ta	ble for cohort studi	BMJ	Open	d by copyright,	/bmjopen-2025		
1							yright,	n-2025		
2 3 4 5	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt n group = u prevalence n	占 Banalysis (95%)	Increase in cancer prevalence	Risk of bias verdict
6 7 8 9	Asgari	2017	USA	Ever exposed	Kaiser permanente consortium	14008 (92.5 per 100,000 person years)	48 (67.4 per of HF 100,000 person 5 g years) 5 g	A nadjusted = 0.68 0.51-0.90); HR djusted: 0.77 (0.58-102)	No, decrease	Good
10 11 12 13 14	Lin	2018	Taiwan	Bipolar disorder	Patients treated with anticonvulsants who did not use lithuim	48/1850 (2.6%)	Superior Sup	1(0.6-1.6)	No	Good
15 16 17 18	Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	19/609 (3.12%) 19/609 (3.12%)	⇒	No	Good.
19 20 21 22 -	George	2019	USA	Antiphysicotic medication	Postmenopausal women not treated with lithium	10079/155095 (6.5%)	ng, . 18/326 (5.5%) A trai	92 (0.58-1.46)	No	Good
23 24	Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	היק 6 patients (1.6%)يق ه	26 (0.186-0.975)	No, decrease	Good
25 26 27 28	Kessing	2015	Denmark	Psychiatric	Randomly selected sample from Danish population	Total amount of subjects: 24.272	(0.86%)	وم end test: HR = 1.01 (0.97-1.05)	No	Good
29 30 31 32 33	Kessing	2024	Denmark	Psychiatric	Lamotrigine use	Cohort 1: 4,281 (18.7%) Cohort 2: 71,069 (21.4%)	Cohort 1: 4,496 hoo (15.8%) Cohort 2: 13,422 gi (18.3%) s	Rsk difference= Cohort 1: -2.8% (- 2 9.7%; 4.1%) Cohort 2: -3.0% (- 2 6.0%; -0.1%)	No	Good
34 35 36 37	Martinsson	2016	Sweden	Psychiatric	General population compared to Bipolar disorder (with and without lithium)	166,443 (6.4%)		gence 804 (0.89-1.23)	No	Good
38 39	Zaidan	2014	France	Bipolar disorder	Matched ( EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	bliograp	Yes	Poor
40 - 41 42 43 44				For	oeer review only - http://bmjope	n.bmj.com/site/abou	ıt/guidelines.xhtml	hique de l		

Table 5. Data extraction and results table for case-control s	tudies on the use of lithium
Table 5. Data extraction and results table for case-control s	tudies of the use of fithium

						BMJ Oper	1	d by copyright, incode		Page 48 of 6
1 2	Table 5. Data	extractio	on and resul	ts table for ca	ase-control studies on the use	e of lithium		right,		
2 3 4	Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer	Risk of bias verdict
5 6 7 8	Hallas	2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	1.19 (1.03-1.39) So may 1.19 (1.03-1.39) So may uses	Yes, minimal (not all data shown, not the main	Poor
9 10 11 12	Kahan	2018	Israel	Bipolar disorder	All members if LHS (Health insurance company)	Expected cancer cases: 68	Expected cases Lithium group: 61.09	standardize	No No	Poor
13 14 15 16 17 18 19	Li	2024	Taiwan	Psychiatric	Matched controls	15,540 matched controls	45 cases exposed (9.1%) 1470 cases unexposed (9.1%)	1.25 (0.91-1.60) Superior ext and ext and or or OR = 0.81 (0.93) 1.12); p=0.200 (ABES) 1.12); p=0.200 (ABES) 1.12); p=0.200 (ABES) 1.12); p=0.200 (ABES)	No	Good
20	Pottengard	2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	ی بوری ایران کی ایرا	No	Good
21 22 23	Pottengard	2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	OR = 1.3 (0.7-2)	No	Good
23 24 25 26	Tamim	2008	Canada	Psychiatric	No history of cancer	257 (0.8%)	69 (0.9%);	No significant difference	No	Poor
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44					For peer review only - h	ttp://bmjopen.bmj	.com/site/about	No significant difference OR not reported OR of reported iar technologies.		

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Pag	je 49 of 60 Table 6. D	ata extract	ion and result	s table for coho	ort studies on the	e use of cimetidine	BMJ Open e		in i/bmjopen-202		
1 2 3 4	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	ght, Increase in ncrease in clugregalence	Exposure duration	Risk of bias verdict
5 6	Moller	1989	Denmark	Gastro- intestinal	No control, na	tional incidence		RR= 1.5 (p<0.001)	ng for ny es	not specified	Poor
7 8 9 10	Rossing	2000	USA, western Washington State	Gastro- intestinal	All males/females in the area	Total cohort = 48.512 users. Cases not shown	267 cimetidine Cases	0.9 (0.8–1.1)	30 May 2025. Enseigner uses relate	not specified	Good, however not all data shown.
11 12 13 14 15	Velicer	2006	USA	Gastro- intestinal	Victims and lifestyle cohort	478 (1.8%) (incidence=7.6)	20 (1.6%)(incidence is 8.5)	RR= 0.97 (0.61- 1.53)	Dowfiloade nent Superi d to text an	not specified	Fair
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44							20 (1.6%)(incidence is 8.5)		2025 at Agence Bibliographique de ologies.		

Study Colin jones Colin jones Coogan	Year 1991 1985 2005	Location UK UK	Indication for use Gastro- intestinal Gastro-	Control condition X	Controls	Cases	/bmjopen-2025-1032 d by copyright, including	Increase in cancer	Risk of bias
Colin jones Coogan	1985	UK	intestinal Gastro-	x				prevalence	verdict
Coogan					х	111/9928 (1.1%)	for a u NO control group!	No	Poor
	2005		intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	is sel regn 20 regn 20	No	N/A
		USA	Gastro- intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	6 9 9 6 9 9 6 9 9 6 9 9	No	Poor
Holly	1997	USA	Gastro- intestinal	Never use	х	х	for uses and the second	Decrease	Poor
Mathes	2008	USA	Gastro- intestinal	Never users	n= 1390, 1136 (92.5%) unexposed; 92 5(7.5%) ever use; 36 (2.9%) > 2 years	Ductal carcinoma: n=1148; 939 (92.1%) never use; 81 (7.9%) ever use; 27 (2.6%)>2 years of use	Ever use 1.5); Logula carcinoma OR = 1.1 (0.8- 1.5); Logula carcinoma OR = 1.0 (0.7- 1.6); >2 pears use ductal carcinoma, 0.9 (0.5-1.5); obgar carcinoma, 1.1(0.6-1.9)	No	Good
Moller	1992	Denmark	Gastro- intestinal		controls Group	191	<b>9</b> <b>0</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	No	Poor
Schumacher	1990	USA	gastro- intestinal	Non users	x	x	OB:= 2=1 (95% CI = 0.7-6.3)	No	Poor
			<b>-</b>				Agence Bibliographique de		
	Moller	Moller 1992	Moller 1992 Denmark	Mathes2008USAGastro- intestinalMoller1992DenmarkGastro- intestinalSchumacher1990USAgastro- intestinal	Mathes2008USAGastro- intestinalNever usersMoller1992DenmarkGastro- intestinalMatched health na gastro- intestinalSchumacher1990USAgastro- intestinalNon users	Mathes2008USAGastro- intestinalNever usersunexposed; 92 5(7.5%) ever use; 36 (2.9%) > 2 yearsMoller1992DenmarkGastro- intestinalMatched controls Group health national pharmacySchumacher1990USAgastro- intestinalNon usersx	Mathes2008USAGastro- intestinalNever usersunexposed; 92 5(7.5%) ever use; 36 (2.9%) >2 yearsDuctal carcinoma: n=1148; 939 (92.1%) never use; 81 (7.9%) ever use; 27 36 (2.9%) >2 years of yearsMoller1992DenmarkGastro- intestinalMatched controls Group health national pharmacySchumacher1990USAgastro- intestinalNon usersxx	Mathes       2008       USA       Gastro- intestinal       Never users       unexposed; 92 5(7.5%) ever use; 36 (2.9%) > 2       Ductal carcinoma: (92.5%)       Ever use; ever use; 81 (7.9%)       Ever use; 1.5); Logular carcinoma OR = 1.0 (0.7- 1.6); > 2         Moller       1992       Denmark       Gastro- intestinal       Matched controls Group health national pharmacy       Use       0.5-1.5); Dobgar carcinoma, 1.1(0.6-1.9); use         Schumacher       1990       USA       gastro- intestinal       Mol users       x       x       Object = 2.1 (0.7-6.3)         Schumacher       1990       USA       gastro- intestinal       Non users       x       x       Object = 0.7-6.3)	Mathes       2008       USA       Gastro-intestinal       Never unexposed; 92 users       0.00000000000000000000000000000000000

age 51 of 60 Table 8. Data	extraction a	and results ta	ble for cohort stu	udies on the use c		Open lozapine, and olanzapin	vbmjopen-2025-10329، م d by copyright, including Analysis		
Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence		Increase in cancer prevalence	Risk of bias verdict
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	9 30 HR = 1.05 50 A2 1.21 5 50 A2 1.21 5 50 A2	No	Good
0 1 2 Tiihonen 3 4	2022	Finland	Clozapine (schizophrenia)	matched controls (schizophrenia patient without cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted O	Yes, hematologic	Good
6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6							2025 at Au hologies.		
7 8 9 0 1 2 3 4 5			F	or peer review only	/ - http://bmjoper	n.bmj.com/site/about/gui	gence Bibliographique de I idelines.xhtml		

Study	Year	Location	Drug of interest	Control condition	Controls	Cases	/bmjopen-2025-03296 d by copyright, 1955-03296 AnalysisTecludir	Increase in cancer prevalence	Risk o bias verdic									
Brainerd	2024	USA	Clozapine	Matched controls	23,043 (4.1%)	2,306(5.3%)	OR = 1.31 (608-6.60)	Yes	Good									
		_	Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% C) is 875 (1.31–293)	yes										
Chen	2022	Taiwan	Olanzapine	Matched controls	63/37908	13/9502	OR (95% C)) (0.38-25)	no	Good									
			Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% <b>ຢິ່ງອື່າ 5</b> 4 (0.56– <b>ລ</b> ີສິງຊ	no										
				Not treated with	39553/1962602 (2.0%)	4/352 (1.1%)	ତମ = 0.54 (୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦	No										
Friedman	2020	USA	Haloperidol	haloperidol	576	4/576 (0.7%)	OR = 0.32 (0916-60.84)	No, decrease	Good									
					2008	30/2008 (1.5%)	OR = 0.69 (0 4 4 4 4 4 5 4 5 4 5 4 5 4 5 4 5 4 5 4	No, decrease										
		_	Clozapine	Non-gastric cancer	92 (0.06%)	4 (0.01%)	OR = 0.35 (	No, decrease										
Hsieh	2019 Taiwan	2019 Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Taiwan	Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (0 14-9.46)	No, decrease	N/A
			Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (505 05 0.35)	No, decrease										
Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted Of 1:3:30 (1.09-1656) Adjusted Of 2:5:15 (0.9-137)	No in fully adjusted model (2), yes when only adjusted for age and gender	Good									
Tiihonen	2022	Finland	Clozapine	No cancer	3734 matched controls (9.9used clozapine%)	375 cases; 19,5% used clozapine.	aOR = 2.94 (nor 107 - 2025) aOR = 2.94 (nor 107 - 2025) at Ag	Yes, hematologic cancers	Good									
				For peer review c	only - http://bmjopen.l	bmj.com/site/about/gui	ence Bibliographique de											

# Page 53 of 60

44 45 46

ge 53 of 60 Table 10. Data extraction and results table for pharmacovigilance and database studies on the use of haloperidol, clozapine and olanzapine

Study	Year	Drug of interest	Control condition	Type of cancer	Cancer risk Wnt group = prevalence	right, in Aalysis (95%)	Increase in cancer prevalence	Risk of bia verdict	
		Clozapine	х	Pituary tumor	17 cases		No		
Lertxundi	2019	Haloperidol	х	Pituary tumor	11 cases	₫ RR = 7.0(4.35-11.3)	Possibly	N/A	
		Olanzapine	x	Pituary tumor	17 cases	<b>ឆ្</b> ̃R∰ <b>≥</b> 2.53 (1.57-4.1)	Possibly		
		Clozapine	х	Pituary tumor	4 cases	0.9 (0.4-1.7)	No		
Szarfman	2006	Haloperidol	х	Pituary tumor	9 cases	a A R R = 5.6 (2.9-13)	Possibly	N/A	
		Olanzapine	x	Pituary tumor	11 cases	2.3 (1.4-3.7)	Possibly		
	2024	Clozapine	x	Hematologic malignancies	275	aRe 5.14 (7.75-10.77)	Possibly		
Chretien	2021	Olanzapine	x	Hematologic malignancies	68	aR 20.88 (0.66- 1.16)	No	N/A	
Maashima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1 000 (0.07, 3.51) ROR	No	NI/A	
Maeshima	2021	Olanzapine	х	Benign and malignant breast cancer	1825	239.91 (0.07, 3.51) ROR	No	N/A	
Dawson	2023	Clozapine	х	Hematological	104/384	excess of hematological cancers in people expozed to clozapine	Possibly		
				Neoplasm	61/384	l tra	No		
				Lung	50*384	en.t	No		
				Breast	37/384	jų, mj	No		
				Colorectal	28/384	n.bmj.com/ ning, and si	No		
				Brain	18/384	open.bmj.com/ on June 8, 2025 at training, and similar technologies	No		
				Skin	17/384	n Juliar	No	N1/A	
				Esophagogastric	11/384	June lar tec	No	N/A	
				Pancreatic	10/384	8, N	No		
				Urological	9/384	2025	No		
				Testicular	8/384	jies	No		
				Hepatic	7/384	at Agence les.	No		
				ENT	6/384	enc	No		
				Gynecological	<5/384	e B	No		
				others	14/384	Biblic	No		
Uwai	2024	Clozapine	х	All non-hematologic malignancies	1668	Reporti <b>ब्रि</b> Odds Ratio= 1.28 च् <u>र</u> .22-1.34)	Possibly	N/A	

#### Table 11. Critical appraisal table for cohort studies on the use of VPA

1 2	able 11. Ci	ritical ar	opraisal table fo	or cohort studie	es on the use of VPA	BM.	J Open	d by copyright, includin d by copyright, includin to fts - Compari <b>t</b>			F	Page 54 of 6
3 4						Selection (max 1 star)		03296 cludir	(m	Dutcome nax 1 star)		
5 6 7 8 9	Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	(max 2 stars)	Ascertainment of outcome	Long enough follow up	Adequace of follow up	Verdict
10 11	Chavez	2020	Retrospective cohort		*	*	*	/ 2025. D seigneme related *	*	*		Good
12 13	Lin	2018	retrospective cohort study	*	*	*	*	Downloaded ent Superieu to text and * * *	*	*		Good
14 15	Huang	2016	retrospective cohort study	*	*	*	*	paded t and *	*	*	*	Good
16 17 18	Каае	2010	population- based cohort study	*	*	*	*	from htt ur (ABES data min * *	*	*	*	Good
19 20	Kang	2014	retrospective cohort study		*	*	*	⊐~ <mark>ĕ</mark>	*	*	*	Good
21 22 23 24	Singh	2011	cohort study	*	*	*	*	//bmjopen.bmj.com/ g, Al training, and s * * * *	*	*	*	Good
25 26	Yang	2022	Nationwide cohort	*	*	*		and si *	*	*	*	Good
27 28							C	, and similar te				

une 8, 2025 at Agence Bibliographique de l technologies.

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Author         Year         Type of study         Adequary of case definition of the cases         Selection of of the cases         Comparability (max 2 stars)         Outcome (max 1 star)         Outcome (max 1 star)         Verdict           eorge         2023         case-control         *         *         *         *         *         Good           alias         2009         case control         *         *         *         *         *         *         Good           Li         2024         Neted Case control         *         *         *         *         *         *         *         *         Good           tensen         2019         nested Case control         *         *         *         *         *         *         *         *         *         *         Good           tensen         2019         nested Case control         *	e 55 of 60 able 12. Critical	apprais	al table for case c	ontrol studies on t	he use of V		MJ Open	а ву сору	/bmjopen			
definition     of the cases     controls     control     <					Selection	ı	Compai (max 2	rability fight, stars) ,	ت 1-2025-10	max 1 s		
eorge       2023       case-control       *	Author	Year	Type of study	· · · · ·	ativeness of the	Selection of	Definition of controls	controls	Butc Ens	t of	response	Verdict
Agence	George	2023	case-control	*	*	*	*	** late	* 2025 eigne	<	*	Good
Agence	Hallas	2009	case control	*	*	*	*	** 01 01 02	. Dov	٢	*	
Agence	Li	2024		*	*	*	*	** Xt ar	* vnload t Supe	٢	*	
Agence	Kristensen	2019		*	*	*	*	*	* ed fror rieur ( <i>/</i>	¢	*	Good
Agence	Salminen	2016	case-control	*	*	*	*	** 3	n htt BES	<	*	Good
Agence	Stritzelberger	2020		N/A High ri	isk of bias, n	ot the aim of the	study and not all data sho	own A	p://bm 5) .			Poor
Agence	Tilhonen	2022	case-control	*	*	*	*	** 17	jope *	¢	*	Good
io graphiqu hiqu								ng, and similar technologies.	⋗			
				For pe	er review or	nly - http://bmjo	pen.bmj.com/site/about/g	uidelines.xhtml	de I			

					Selection nax 1 star)		d by copyright, includ	/bmjopen-2025-103296	Outcome (max 1 sta		
Author	Year	Type of study	Representatitveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparibility ຜູ້ cohorts of (max 2 stars) ແ	Ascertain Ascertain Ment of Mutcome	n Long enough e follow up	Adequace of follow up	Verdict
Asgari	2017	retrospectiv e cohort		*	*	*	*	* 5. Down	*	*	Good
Lin	2018	retrospectiv e cohort study	*	*	*	*	ext and d *	* nloaded f	*		Good
Cohen	1998		*	*	*	*	lata n ** a	r (AB	*	*	Good
George	2019	restrospectiv e cohort study	*	*	*	*	mining, Al **	* http://bmj	*		Good
Huang	2016	retrospectiv e cohort study	*	*	*	*	training, a *	* * * * * * * * * * 2025. Downloaded from http://bmjopen.bmj.com/ on June 8,	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	and similar technologies. * * * *	* *	*		Good
Kessing	2024	Cohort (Population based)	*	*	*	*	ar technolo *		*	*	Good
Martinsson	2016	Cohort nationwide		*	*	*	ogies. **	* 2025 at Aç	*	*	Good
Zaidan	2014	retrospective cohort study		ort compar	ed to general po	opulation, expressed as	s standardized inc <sup>i</sup>	genced Biblio	io; small cohor	rt	Poor

AuthorYearType of studyRepresent Adequacy of case definitionSelection of controlsDefinition of controlsComparability cases and controlsNon- response rateNon- response rateVerd response rateHallas2009case control****PolKahan2018Case-control study from large databaseData from large database, scale non-applicable, high risk of bit ange database****	Author       Year       Type of study       Represent Adequacy of case definition       Represent of the cases       Selection of controls       Definition of controls       Comparability cases and controls       Represent cases and controls       Non- response cases       Non- response       Non- response <t< th=""><th></th><th></th><th></th><th></th><th></th><th>Selection (max 1 star) omparability</th><th></th><th>Comparability (Max 2 stars)</th><th>for</th><th>(max 1 s</th><th></th><th></th></t<>						Selection (max 1 star) omparability		Comparability (Max 2 stars)	for	(max 1 s		
Hallas       2009       case control       *	Tamim 2008 Nested case- * * * * * question of to study to	Author	Year	Type of study		ativeness	Selection of		Comparability of cases and	mayazuz: Enseign usestrelat	scertain nent of	response	Verdic
Kahan       2018       Case-control study from large database       Data from large database, scale non-applicable, high risk of bight risk	Tamim 2008 Nested case- * * * * * question of to study to	Hallas	2009	case control	*	*		*		iload Super	*	*	Poor
Li2024Nested Case control** <td>Tamim 2008 Nested case- * * * * * question of to study to</td> <td>Kahan</td> <td>2018</td> <td>study from</td> <td></td> <td>Dat</td> <td>a from large dat</td> <td>abase, scale non-applicab</td> <td>le, high risk of bia</td> <td>ed trom n ieur (ABE id datta m</td> <td></td> <td></td> <td>Poor</td>	Tamim 2008 Nested case- * * * * * question of to study to	Kahan	2018	study from		Dat	a from large dat	abase, scale non-applicab	le, high risk of bia	ed trom n ieur (ABE id datta m			Poor
Nationwide       Nationwide <td>Tamim 2008 Nested case- * * * * * question of to study to</td> <td>Li</td> <td>2024</td> <td></td> <td>*</td> <td>*</td> <td>*</td> <td>*</td> <td>**</td> <td>ES) . ining, <i>F</i></td> <td>*</td> <td>*</td> <td>Good</td>	Tamim 2008 Nested case- * * * * * question of to study to	Li	2024		*	*	*	*	**	ES) . ining, <i>F</i>	*	*	Good
Pottengard     2016 (2)     study     * <td< td=""><td>Tamim 2008 Nested case- * * * * * question of to study to</td><td>Pottengard</td><td>2016 (1)</td><td>case control</td><td>*</td><td>*</td><td>*</td><td>*</td><td>**</td><td>njopen.b VI trainin</td><td>*</td><td>*</td><td>Poor</td></td<>	Tamim 2008 Nested case- * * * * * question of to study to	Pottengard	2016 (1)	case control	*	*	*	*	**	njopen.b VI trainin	*	*	Poor
	Tamim 2008 Nested case- * * * * * question of to study to	Pottengard	2016 (2)	study	*	*	*	*	**	mj.com/ g, and sii	*	*	Good
Tamim 2008 control con	ologies.	Tamim	2008		*				Lithium not ma question of study	on June 8, mi <u>t</u> ar techr		*	Poor

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				Selecti	ion (max 1 star)				Dutcome (max	1 star)	
Author	Year	Type of study	Representatitvenes s of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability ( cohorts (max 2 stars)	Scertain Scertain Scertain Scertain	Long enough follow up	Adequace of follow up	Verdi
Moller	1989	Cohort	No control, high risk o	of bias				25. Dov nemen			Роо
Rossing	2000	Retrospective cohort study	*	*		*	**	ay 2025. Downloaded fro nseignement Superieur ( es related to text and dat	*	*	Goo
Velicer	2006	Cohort study		*		*	**	* * rieur ( nd dat	*	*	Fair
							ļ	/bmjopen.bmj.com g, Al training, and :			
						*	0	om http://bmjopen.bmj.com/ on June 8, 20; (ABES) . (ta mining, Al training, and similar technolc			
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							0	2025 at A lologies.			

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					Selection (max 1 star)		t by copyright, Comparibility (Max 2 stars)	$\cdots$ $\underset{\omega}{\simeq}$ (max 1 s		
Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of	Definition of controls	Comparability of cases and controls	Rescertain	Non- response rate	Vero
Colin Jones	1985	case control study	No representativ	e outcome;	already had gast	trcic ulcers, only age and s	ex matched cont	5. Dow		Po
Colin Jones	1991	surveillance study	No control, N/A				text ar	vnload Supe		N/
Coogan	2005	Database study/case- control	*		*		nd data m *	ed from I rieur (AB		Po
Holly	1997	population- based case- control study				*	** **	* * ES) .		Ро
Mathes	2008	Population based case- control study	*	*	*	*	training **	; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;		Go
Moller	1992	Case-control study	High risk of bias			trcic ulcers, only age and s	, and simil	nj.com/ on		Ро
Schumacher	1990	Case-control study	*	*			ar technologies. *	June 8, 20		Ро
							ogies.	5 at A		
								gence Bibliographique de l		
								liograp		
								aphiqu		

45 46

able 17. (	Critical a	appraisal table	for cohort stud	ies on the use of halo		J Open and olanzapine	/bmjopen-⁄ 1 by copyri			
					Selection (max 1 star)		/bmjopen-2025-103296 gn 4 by copyright, includin <b>ie</b> fi	(1	Outcome nax 1 star)	
Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Ascertainment of outcome	Long enough follow up	Adequa of follo up
Tilhonen	2022	cohort study	*	*	*		2025. D eignem related *	*	*	
Wang	2002	Retrospective cohort	*		*	*			*	*
						**	ownloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique ant Superieur (ABES) . to text and data mining, AI training, and similar technologies. *			

Verdict

Good

Good

Page 61	of 60
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				Selectio (max 1 st			Comparibilit (max 2 star	ozeo Iopelin	n.		
Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	Comparibility of		certain	Non- response rate	Verdic
Brainerd	2024	Case Control study	*	*	*	*	**	nent Sud to tex	*	*	Good
Chen	2022	Case-control study	*	*	*	*	* *	perieur t and d	*	*	Good
Friedman	2020	Case-control	*	*	*	*	* *	(ABES ata min	*	*	Good
Hsieh	2005	Database study/case- control		Sc	cale not fully app	licable due to study desig	n, high risk of bia	) . ) . ing, <b>A</b> l tra			Poor; N <sub>/</sub>
Pottengard	1997	population- based case- control study	*	*	*	*	**	aning, ar	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	licable due to study desig *	**	nd similar	*	*	Good
								technologies.	Pertone		
								, an anhiide ifioilidia an			

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## Cancer prevalence after exposure to Wnt-activating drugs: a systematic review

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Manuscript ID	bmjopen-2025-103296.R1
Article Type:	Original research
Date Submitted by the Author:	06-May-2025
Complete List of Authors:	aLKASHAF, AhmeD; University Medical Centre Utrecht Smith-Cortinez, Natalia; University Medical Centre Utrecht Fenton , Georgina; University Medical Centre Utrecht Bok, Sebastian; University Medical Centre Utrecht Stokroos, Robert; University Medical Center Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Stegeman, Inge; University Medical Center Utrecht, Department of Otorhinolaryngology, Head and Neck Surgery Straatman, Louise; University Medical Centre Utrecht, Otorhinolaryngology
<b>Primary Subject Heading</b> :	Oncology
Secondary Subject Heading:	Epidemiology, Oncology
Keywords:	Prevalence, Epidemiology < ONCOLOGY, ONCOLOGY





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- Cancer prevalence after exposure to Wnt-activating drugs: a systematic review
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  - Abstract

- **Objectives:** To assess whether treatment with drugs that activate the Wnt pathway leads to an increased risk of cancer.
- **Design:** Systematic review reported using PRISMA reporting guidelines.
- Data sources: PubMed, Embase and the Cochrane Library were searched through 1 November 2024.
- Eligibility criteria: All primary research articles reporting clinical studies, including observational and experimental studies were included in this review. All studies were eligible for inclusion if they included the exposure of interest, i.e. compounds which have been described to activate the Wnt pathway, and the outcome of interest, i.e. cancer prevalence. No language restrictions were performed.
- Data extraction and synthesis: This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. The search string, objectives, and study protocol methods were defined before the study was initiated.
- **Results:** A total of 48 studies investigating drugs that activate the Wnt pathway (valproic acid, lithium, cimetidine, olanzapine, clozapine, haloperidol) were included in this systematic review. The results from this systematic review show that, at least for the included compounds in the currently used systemic dosage, cancer prevalence does not significantly increase.
- **Conclusions:** The current study found that the use of drugs that activate the Wnt pathway was not associated with an increased risk of cancer. As a promising agent in the regenerative therapy field, further research into Wnt activation as a treatment option should be explored.
  - Study registration: PROSPERO, CRD42021286193.

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2 3 4	35	
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7 8 9	37	Keywords: Wnt activating drugs; cancer prevalence; lithium; valproic acid.
10 11	38	
12 13	39	
14 15	40	Strengths and limitations of this study
16	41	<ul> <li>Inclusion of all study designs, providing a broad overview of studies covering the topic.</li> </ul>
17 18 19 20	42 43	<ul> <li>Substantial heterogeneity in study designs, inclusion of types of patients, and conditions.</li> </ul>
20 21 22 23	44 45	<ul> <li>We cannot generalize the outcomes based on the broad mechanism of action of the compounds included.</li> </ul>
24	46	
25 26	47	List of abbreviations
27 28	48	GSK 3, glycogen synthase kinase 3
29 30	49	HR, hazard ratio
31 32	50	MDS, myelodysplastic syndrome
33 34	51	OR, odds ratio
35 36	52	RR, risk ratio
37 38	53	SLE, systematic lupus erythematosus
39 40	54	VPA, valproic acid Wnt, Wnt/Beta-catenin signaling pathway
41 42	55	Wnt, Wnt/Beta-catenin signaling pathway
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### 56 INTRODUCTION

The Wnt/ $\beta$ -catenin pathway is a signaling cascade that controls cell proliferation, cell polarity, and cell fate determination during embryonic development and tissue homeostasis [1]. Wnt/β-catenin signaling is known to be involved in development of multiple tissues, including brain, eye, ear, spinal cord, bone cartilage among many others [2]. In adulthood crucial roles in the function of intestine, bone and skin have been described for Wnt/β-catenin signaling [2]. Wnts (the ligands that activate the Wnt/β-catenin signaling pathway) are growth stimulatory factors that ultimately lead to cell proliferation. Importantly, dysregulated Wnt signaling has been associated with several diseases such as degenerative diseases [1], neurodegenerative disorders [3-5] schizophrenia [5], aging-related tissue fibrosis [6], autoimmune diseases [7] and many types of cancer [8-12]. 

Currently, targeting the Wnt/ $\beta$ -catenin signalling pathway, either by activating or inhibiting it, is being researched as therapy for some types of cancer [13,14], neurodegenerative diseases [15-18], hair loss [19,20]. When therapeutic agents target crucial developmental signaling pathways (such as Wnt, Notch, Hedgehog and bone morphogenic protein (BMP) pathways) serious and devastating effects on embryogenesis and carcinogenesis might arise due to increased cell proliferation. In line, continued activation of the Wnt pathway has been associated with therapy resistance in cancer patients and has been shown to promote self-renewal of cancer cells [21]. Unfortunately, the effect of Wnt activation on cancer prevalence has not been consistently studied. In the last 15 years, common drugs used in the clinic have been described to activate the Wnt pathway [22,23]. The most common Wnt activators used in the clinic are lithium and valproic acid (VPA), which have been used as treatment for psychiatric disorders since the 1960's [24-26]. Besides, many novel therapeutic drugs have been synthesized specifically to activate Wnt in the last 10 years and are used in the clinic [27]. Many of these drugs activate the Wnt signaling pathway through the inhibition of glycogen synthase kinase 3 (GSK3) [28]. This is one the most well studied mechanisms for activating the Wnt signaling pathway [28]. 

There are many novel therapeutic drugs in development for clinical usage that activate the Wnt pathway. However, safety concerns regarding its activation remain [29]. Therefore, we conducted a systematic review to address the association between the use of drugs that activate the Wnt pathway and prevalence of any type of malignancy in the clinic. Our aim was to assess whether treatment with drugs that activate Wnt leads to an increased risk of cancer. 

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## <sup>3</sup> 92 **METHODS**

We evaluated all data available on clinical use of Wnt activators following the Prisma 2020 writing guideline for systematic reviews [30]. PICO framework was used to improve the search strategy [31]. The outcome of interest was the prevalence of any cancer, malignancy, or neoplasm, regardless of age, sex, and geographic location. The exposure of interest was any compound activating the Wnt pathway, regardless of indication, dosage and duration. An overview of the included compounds and their mechanism of action is available in Table 1. 

## <sup>14</sup> 100 Search strategy

The final search was done on November 1<sup>st</sup>, 2024. PubMed, Embase and Cochrane databases were searched. All articles until November 1<sup>st</sup> were included in the search. On Embase, conference abstracts and reviews were removed. No further search filters were used. No language restrictions were applied. The search syntax consisted of names of medication with known Wnt activating properties used in the clinic combined with synonyms for 'cancer'. The full search strategy can be found in Table S1. 

### 24 107 Article selection

All primary research articles reporting clinical studies, including observational and experimental studies were included in this review. Studies were eligible for inclusion if they included the exposure of interest, i.e. compounds which have been described to activate the Wnt pathway, and the outcome of interest, i.e. cancer prevalence. Patients of all ages were eligible for this study. No control group was required. Articles assessing compounds with no clear Wnt activating properties were excluded. Animal studies, in vitro studies and non-primary research articles like review articles and letters were excluded. Two independent reviewers (A.A., G.F. N.S-C, S.B.) screened title and abstracts of collected studies after duplicate removal for eligibility criteria. Discrepancies were resolved by discussion between the two reviewers until a consensus was reached. Full text screening was performed by two independent reviewers and disagreements were solved as above. Rayyan systematic review tool [32] was used to semi-automate the primary screening. 

### 42 121 Data extraction

A data extraction table was used to extract study characteristics and findings by two reviewers (A.A., N.S-C) with the software Microsoft Excel. Data extraction was performed by one reviewer and checked by another reviewer. Discrepancies were solved by discussion between the two reviewers until a consensus was reached. The data extraction table included the following information: Study, indication for intervention, population, age, geographical location, used Wnt activator, used control group, cancer prevalence and cancer type (Tables S2-S10). No authors were contacted due to data unavailability after inclusion. 

## <sup>3</sup><sub>4</sub> 130 *Critical appraisal*

The methodological quality of included articles was assessed by two reviewers (AA. N.SC) using the Newcastle Ottawa-Scale (NOS) for nonrandomized studies as a reference
guide [33]. Risk of bias assessment was performed by one reviewer and checked by
another reviewer. Risk of bias in cohort studies was assessed for the following domains:

- $_{10}^{9}$  135 selection bias, comparability of cohorts, and outcome (**Tables S11-S18**).
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## 1213 137 Effect measures

14 138 Results were expressed according to the reported ratios from the published studies. This 15 139 includes percentages, odds ratios (OR), risk ratio's (RR) and hazard ratio's (HR), in 16 140 accordance with study design and available data. When unavailable, RR's and OR's were 17 141 calculated. All ratios were used to answer the main questions qualitatively. No quantitative 18 19 142 analyses were conducted for this systematic review. 20 143

- <sup>22</sup> 144 *Study registration*
- <sup>24</sup> 145 PROSPERO, CRD42021286193.
- 26 146 27

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- 147 Patient and public involvement
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- 30 148 None.
- 31 32 149
- <sup>33</sup> 34 150 **RESULTS**
- <sup>35</sup> <sub>36</sub> 151 Article selection

152 Our PubMed database search until November 2023 yielded a total of 25969 articles. After 37 38 duplicate removal, 20,427 articles remained, that were screened for title and abstract. 153 39 154 Following title and abstract screening, 172 articles were eligible for full text screening. All 40 155 172 articles could be retrieved. After full text screening, 48 studies were included for this 41 review. Main reasons for exclusion were outcome that was not in our inclusion criteria, 156 42 43 publication type, study design, population, and different drug. Article screening is 157 44 summarized in the flowchart in Figure 1. 158 45

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<sup>46</sup> 159 Study characteristics

47 160 Included studies, which are summarized in Tables S2-S10, consisted of 21 cohort, 19 48 case-control and 8 pharmacovigilance studies. Drugs with reported Wnt activating 161 49 properties included were VPA (13 studies), lithium (15 studies), haloperidol (7 studies), 162 50 51 163 cimetidine (10 studies), clozapine (9 studies), and olanzapine (7 studies). Some studies 52 164 assessed multiple drugs of interest. 53

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167 consisting of 160 countries was included [34]. Most common indications were 168 psychotropic, gastro-intestinal and neurologic use. All compounds were administered 169 systemically in clinical dosing. Most studies assessed any type of cancer prevalence. All 170 studies assessed cancer risk by analyzing clinical data or performing questionnaires. In 171 addition, a few studies included histological verification for cancer diagnosis in addition to 172 clinical data [35–38]. All Wnt activating compounds were used in their clinical dose 173 respective to their indication.

<sup>12</sup> 13 174 *Risk of bias* 

Based on the Newcastle-Ottawa Scale, all but one included study concerning VPA were
 determined to have a low risk of bias (Tables S11&S12). One study by Stritzelberger et
 al. (Table S12) did not show all data concerning VPA [39].

178 Concerning Lithium, for both cohort and case-control studies, most studies were
 179 determined to have low risk of bias (Tables S13&S14). One cohort study by Zaidan et al.
 180 (Table S13) and three case-control studies by Hallas et al., Kahan et al. and Tamim et al.
 181 (Table S14) were subject to a high risk of bias [40–43].

182 Most studies reporting cimetidine use had a high risk of bias (Tables S15&S16). Main
 183 points were missing data, lack of control group or no comparability of groups. The cohort
 184 study by Velicer et al. (Table S15) was determined to be of fair risk of bias [44]. Only the
 185 study by Rossing et al. (Table S15) was determined to be of low risk of bias [44].

30 186 For haloperidol, both the cohort study by Wang et al. (Table S17) and the case-control 31 187 study by Friedman et al. (Table S18) were determined to have low risk of bias [73, 74]. 32 188 The risk of bias in the case-control study by Hsieh et al. (Table S18), was high because 33 189 they used non-gastric cancers as a control for gastric cancer instead of healthy individuals 34 35 190 with no cancer [75]. The case-control study by Pottengard et al. (Table S18) was 36 191 determined to be of good quality [37]. 37

- <sup>38</sup> 192 *Outcomes*
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194 VPA

42 195 Seven cohort studies assessed the association between VPA use and cancer prevalence 43 196 [35,45–50]. 6 studies showed no statistically significant difference in cancer prevalence 44 197 between exposed versus controlled subjects respectively ([46], RR = 0.877 (0.642 - 1.032); 45 46 198 [47], RR=1.18 (0.96–1.46); [48], RR= 0.848 (0.563-1.277); [50], RR= 0.848 (0.563-1.277); 47 [35], HR = 0.96 (0.84-1.19) 1.0 (0.8-1.3) 1.0 (0.7-1.3); [49], RR= 1 (0.7-1.3)). The study 199 48 200 by Chavez et al. evaluated melanoma prevalence in VPA exposed individuals. In this 49 201 study, VPA exposed individuals had a significantly reduced prevalence of melanoma 50 51 202 compared to controls ([51] HR = 0.64 (0.51-0.79)). 52

Additionally, 6 case-control studies assessed the association between VPA use and cancer prevalence [38,39,43,52–54]. All studies showed no statistically significant increase in cancer prevalence between exposed versus controlled subjects respectively

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- 206 ([55], OR= 0.85, 0.70-1.04; [43], OR= 1.21 (0.95-1.56); [39], p=0,760; [52], OR= 0.62 207 (0.42-0.92); [38], 0.2% cases and 0.2% control group); [54], OR = 0.58 (0.39-0.56)).
- 208 Lithium

Nine cohort studies assessed the association between lithium use and cancer prevalence, including melanoma, urinary tract tumors, malignant neoplasms, invasive breast cancer and any type of cancer [42,48,49,55-60]. Six studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively ([36], OR=1.19 (0.71-2.01); [57], RR= 1.01 (0.97-1.05); [60], Risk difference = -2.8% (-9.7-4.1) for cohort 1 compared to -3.0% (-6.0-0.1) for cohort 2; [58], RR=1.04 (0.89-1.23); [55], RR= 0.92 (0.58-1.46); [49], RR=1 (0.6-1.6)). Asgari et al. and Huang et al. evaluated cancer risk in lithium exposed individuals compared to controls. In both studies lithium exposed individuals had a significantly reduced cancer risk compared to controls ([56], unadjusted HR=0.68 (0.51-0.90); [48], RR= 0.426 (0.186-0.975)). Zaidan et al., found an increased risk of renal tumors in patients exposed to over 20 years of lithium in comparison to both the general population and to kidney function matched controls (based on glomerular filtration rate) p=0.04 [42]. 

- Additionally, six case-control studies assessed the association between lithium use and cancer prevalence [40,41,43,54,61,62]. five studies showed no statistically significant difference in cancer prevalence between exposed versus controlled subjects respectively ([41], 0.8% versus 0.9% incidence; [62], OR= 1.01 (0.86-1.19) for any use, OR= 1.06 (0.84-1.34) for >5 years use: [40], standardized incidence ratio= 0.93 (0.6-1.38) for male subjects and 1.25 (0.91-1.69) for female subjects; [61], OR = 1.3 (0.7-2.1); [54], OR = 0.81 (0.58-1.12)). Hallas et al. (2009) showed a slight increase in cancer prevalence in subjects with long term exposure to lithium [43], OR = 1.19 (1.03-1.39)).
- 35 230 Cimetidine

Three cohort studies assessed the association between cimetidine use and cancer prevalence [63–65]. The study by Moller et al. did not include a control group [64] The remaining two cohort studies investigated gastrointestinal, breast and prostate cancer risk and found no significant increase in cancer risk in the groups exposed to cimetidine in comparison to controls ([63], RR = 0.97 (0.61-1.53); [65], RR= 0.9 (0.8-1.1) for breast cancer risk in women and RR = 0.7 (0.6-0.8) for prostate cancer in men)). Rossing et al. found a slightly increased risk of prostate cancer in a subgroup of men who had filled >21 prescriptions of cimetidine [65], RR = 1.4 (1.0 - 1.9)). 

Five case-control studies assessed the association between cimetidine use and cancer prevalence [66-70]. In all studies, cimetidine exposed individuals showed no significant difference in ratio compared to controls ([66], OR=0.9 (0.6-1.2); [67], OR = 0.39 (0.17-0.89); [70], ductal carcinoma, ever use: OR= 1.1 (0.8-1.5); >2 years use, 0.9 (0.5-1.5); [69], no analysis reported; [68], OR= 2.1 (0.7-6.3)). Lastly, a cohort study and a surveillance study conducted by Colin Jones et al. showed no increased cancer prevalence after cimetidine exposure [71,72]. 

- <sup>3</sup> 246 Haloperidol

A cohort study by Wang et al. assessed the association between haloperidol use and breast cancer prevalence, including a total of 46,269 women. A breast cancer prevalence of 0.052% (1228 cases in 237242 person-years in control group and 240 cases in 46269 person years in haloperidol group) was found in both exposed and unexposed groups. indicating no significant increase in breast cancer prevalence in women exposed to haloperidol compared to unexposed women [73]. 

Additionally, three case-control studies assessed the association between haloperidol use and cancer prevalence. A case-control study by Friedman et al. found a potential negative association between haloperidol use and prostate cancer risk, compared to controls depending on duration [74], at >2 years of use, OR = 0.54 (0.20–1.44), at >1 year of use OR = 0.32 (0.12–0.84), at <1 year of use, OR = 0.69 (0.48–0.99). Another case-control study by Hsieh et al. found a reduced risk of gastric cancer associated with haloperidol use [75], OR = 0.25 (0.14-0.46). A third, population-based case-control study by Chen et al. assessed the risk of endometrial cancer after exposure to haloperidol and other antipsychotics. For haloperidol, an increase of endometrial cancer after exposure to haloperidol was found [80], OR= 1.75 (1.31-2.34). 

- Three database studies assessed the association between haloperidol use and cancer prevalence. The database study by Maeshima et al. using the Japanese adverse drug event database showed no increased risk of breast cancer in women exposed to haloperidol [77], ROR = 0.49 (0.07-3.51). However, the study by Lertxundi et al. using the European pharmacovigilance database showed a possible increased risk of pituitary tumors of subjects exposed to haloperidol [78], PRR= 7.0 (4.35-11.3). Finally, a pharmacovigilance study using the adverse event reporting database from the U.S.A's food and drug administration by Szarfman et al. suggested a possible increased risk of pituitary tumors in patients exposed to haloperidol [79], ARR= 5.6 (2.9-13).
- <sup>37</sup><sub>38</sub> 272 Olanzapine

Three case-control studies assessed the association between olanzapine use and cancer prevalence. A nationwide case-control study by Pottengard et al. assessed the association between olanzapine use and breast cancer prevalence. Breast cancer cases were verified by histology. This study found a slightly increased risk of estrogen receptor-positive breast cancer in subjects exposed to olanzapine, attributed to its prolactin elevating properties when the study was only adjusted for age and gender [37], aOR= 1.30; 95% CI = 1.09-1.56); however, in the fully adjusted model, no significant increase was found (aOR= 1.15; 95% CI= 0.9-1.47). Another case-control study by Hsieh et al. found a reduced risk of gastric cancer associated with olanzapine use [75] (OR= 0.13 (0.05-0.35)). Lastly, the case-control study by Chen et al. found no increased risk of endometrial cancer after exposure to olanzapine [80] (OR = 1.14 (0.56-2.30)). 

Three database studies assessed the association between olanzapine exposure and cancer prevalence [77–79]. The database study by Maeshima et al. showed no increased risk of breast cancer in women exposed to olanzapine [77] (ROR= 0.51 (0.07-3.51)).

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<sup>3</sup> 287 However, the database studies performed by Lertxundi et al. and Szarfman et al.
 <sup>3</sup> 288 suggested an increased risk of pituitary tumors of subjects exposed to olanzapine [78]
 <sup>6</sup> 289 (PRR= 2.53, (1.57-4.1)); [79] ARR=2.3 (1.4-3.7)).

8 290 Clozapine

One cohort study by Tiihonen et al. assessed the risk of developing hematologic malignancies after exposure to clozapine. A significant, dose dependent, increased risk of hematologic malignancies was found [81] aOR= 3.35 (2.22-5.05) for >5000 defined daily dose cumulative exposure). Four case-control studies assessed the association between clozapine exposure and cancer prevalence. The case-control study by Hsieh et al. assessed the association between clozapine exposure and cancer prevalence and found a reduced risk of gastric cancer associated with clozapine use [75] (OR = 0.35 (0.13-0.97)). The case-control study by Chen et al. found no increase in endometrial cancer risk after exposure to clozapine [80] (OR = 1.14 (0.56-2.30)). The case-control study by Tiihonen et al. found an increased risk of hematologic malignancies after exposure to clozapine [81] (aOR = 2.94 (2.07-4.17)). Interestingly, no significant difference for non-hematologic malignancies were found [81] for clozapine (aOR= 1.47 (1.25-1.47)); as compared to other antipsychotics: (aOR=1.30 (1.15-1.47)). Finally, the case-control study by Brainerd et al. also found an increased prevalence of hematologic malignancies after clozapine exposure in war veterans [82] (OR = 1.31 (1.08-1.60)). 

Additionally, five database studies assessed the association between clozapine exposure and cancer prevalence. Two database studies by Szarfman et al. and Lertuxi et al., assessed the association of clozapine and pituitary tumor prevalence [78,79]. For clozapine, both studies showed no significant increase in pituitary tumor prevalence in subjects exposed to clozapine [79] (ARR= 0.9 (0.4-1.7)); [78] (PRR=0.98 (0.5-1.8)). Two pharmacovigilance studies by Chrétien et al. and Dawson et al. assessed the risk of developing hematologic malignancies in subjects exposed to clozapine, due to the risk of severe haematologic side-effects when using clozapine [34,83]. In the first study, clozapine exposed individuals had a significantly increased prevalence of leukemia aOR = 3.54 (2.97-4.22) and malignant lymphoma, aOR=9.13, (7.75-10.77) compared to controls) [34]. In the second study an excess of hematologic malignancies in subjects exposed to clozapine was reported, indicating a possible increase in cases (no analysis performed) [83]. Finally, a database study by Uwai et al. assessed the risk of non-hematologic malignancies in subjects exposed to clozapine [84]. The study showed a possible relationship between clozapine and multiple non-hematologic malignancies including lung, gastrointestinal, esophageal, throat malignancies and metastases to the spine [84] (Reporting odds ratio = 1.28 (1.22-1.34)). 

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### 52 324 DISCUSSION

The aim of this review was to assess the risk of cancer development after the use of drugs that activate the Wnt pathway in humans. 48 observational studies (**Tables S2-S10**)

analyzing the risk of cancer of 6 different drugs that have known Wnt activating properties were included in this systematic review. The drugs assessed in this review were VPA, lithium, cimetidine, haloperidol, olanzapine, and clozapine. Most of the included studies showed no increase in cancer prevalence after being exposed to Wnt activating drugs. Most notably, are the 18 included cohort studies, which were assessed to have low risk of bias. These studies showed no increased cancer prevalence, and in some cases even a decreased cancer prevalence. These results suggest that using medication that activates the Wnt pathway in patients does not elevate cancer prevalence. 

A few included studies showed an increase in the prevalence of malignancies after usage of Wnt activating drugs. Interestingly, the included studies that showed an increase in cancer prevalence reported increased cancer prevalence for specific cancer types; there was not a systematic increase in cancer risk. The study by Zaidan et al., showed an increased risk of developing solid renal tumors after a median of 20 years of lithium exposure. However, as lithium is known to be nephrotoxic, and no systemic increase in cancer risk was observed, this increase in cancer prevalence could be attributed to direct toxicity, rather than the activation of the Wnt pathway [42]. Chen et al. found an increased risk of endometrial cancer after exposure to haloperidol, attributed to antipsychotic-induced hyperprolactinemia, which is a common side-effect of antipsychotics, and not to the Wnt pathway activation. Of note are both olanzapine and clozapine, which also activate the Wnt pathway, but showed no increase in endometrial cancer risk [80]. 

One study (which had many confounders and a high risk of bias), found an increased prevalence of gastric cancer in patients that had used cimetidine for gastric ulcers compared to the general population [72]. No other included studies reported an increased cancer risk after cimetidine exposure. Therefore, it is not likely that cimetidine is carcinogenic. In this context, patients with gastric ulcers are already at a higher risk of developing gastric cancer [85]. A better control for this study would have been patients with gastric ulcers and no cimetidine use. 

Lastly, and most notably, multiple studies found an increased prevalence of hematologic malignancies in subjects that were exposed to clozapine [34, 81, 83]. Clozapine is well-known as the first second generation (atypical) antipsychotic and gold standard drug for treatment-refractory schizophrenia, but it has many adverse effects. Agranulocytosis is a relatively common and well-known side-effect of clozapine [86]. Bone marrow toxicity has been described in *in vitro* studies [87]. The pathogenesis of clozapine-induced agranulocytosis or bone marrow toxicity is still not clear; however, it is unlikely to be Wnt associated. Multiple alternative hypotheses have been described [86], all non-related to the Wnt pathway activation. In the case-control study performed by Tilhonen et al., they reported no differences in non-hematologic cancer risk for clozapine in comparison to other antipsychotic drugs [81]. Based on available data, we can conclude that subjects exposed to clozapine are at an increased risk of hematologic cancers, due to direct bone marrow damage, unrelated to its Wnt pathway activating properties. The fact that the 

In addition to cohort and case-control studies, multiple pharmacovigilance/surveillance studies were included in this systematic review (Tables S2-S10). The pharmacovigilance/surveillance studies by Lertxundi et al. and Szarfman et al. showed an increased risk of developing pituitary tumors after being exposed to the antipscyhotics haloperidol and olanzapine [78,79]. Nonetheless, this risk was attributed to antipsychotic-induced hyperprolactinemia, which is a common side-effect of antipsychotics, and not to the Wnt pathway activation. None of the included studies showed an increased risk of non-pituitary malignancies. Therefore, we can conclude the increase in cancer risk is not caused by the Wnt activating properties of these drugs. 

378 Strengths and weaknesses of the review
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We assessed the cancer risk of multiple drugs with laboratory proven Wnt pathway activation. Most of the included drugs activate the Wnt pathway through GSK3-Beta inhibition (Table 1) [88,89]. Since the activation of Wnt is not their main therapeutic target, the level of Wnt activation may differ between various drugs. However, to assess all data available on the prevalence of cancer after usage of drugs that activate Wnt, we included all available mechanisms to Wnt activation. This study therefore included all papers available. 

- This systematic review included a complete search of all data available until November
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   34 389 Strengths and weaknesses of the included studies

In this review, a total of 48 studies were included, summing up extensive data on multiple drugs activating the Wnt pathway. Notably, 21 cohort studies were included, of which 18 were assessed to be subject to a low risk of bias. This leads to an extensive dataset on the cancer risk of these compounds. Opposed to the cohort studies, however, the 19 included case control studies involved a wide variety in risk of bias and study methods. Notably the articles regarding cimetidine, which were relatively old overall, showed a high risk of bias. 

- <sup>45</sup> 397 The wide variety in study designs, types of patients, cancer types and used compounds,
   <sup>46</sup> 398 resulting in heterogeneity in the data prevented us from conducting a meta-analysis,
   <sup>47</sup> 399 which results in limitations in drawing an overall conclusion regarding the cancer risk of
   <sup>400</sup> Wnt pathway activation.
- Another limitation is the drugs that were assessed in the included studies of this review. These drugs activate the Wnt pathway, but they are not specifically designed and used for their Wnt activating properties. These drugs have been in use since the 1950's and their Wnt activating properties have been described only in the last 30 years, mainly in in vitro experiments. Novel Wnt activating drugs, like CHIR99021 [90], have been produced

in the past few years. However, given that these drugs have not been used clinically, their risk is not clear and has to be assessed in the future. Furthermore, included studies had considerable missing data, including data to assess dose-related cancer risk, such as duration of treatment and used dosages. In most articles, Wnt activating properties were not discussed. Finally, there were no randomized controlled trials included in this review; only observational studies were included which are by design more at risk of bias due to the lack of randomization. 

#### CONCLUSIONS

Various applications are being researched for both activating and inhibiting the Wnt pathway. Cancer risk, however, remains a big concern [29]. The results from this systematic review show that, at least for the compounds included in the currently used systemic dosage, no increase in cancer prevalence was found in any of the studies included, which could be attributed to Wnt pathway activation. These findings suggest that compounds activating the Wnt pathway are, regarding cancer risk a safe option. 

Before taking this conclusion into medical practice, however, further research on higher dosages, local administration and drugs specifically designed to induce Wnt activation should determine whether the activation of the Wnt pathway is indeed a safe treatment option with regards to cancer risk. 

- In the regenerative therapy field, Wnt activation is a promising agent for future treatment opportunities. Based on the data in this review, we can conclude that Wnt activation by the assessed compounds leads to no increased cancer risk. Therefore, further research into Wnt activation as a treatment option should be explored.

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Ethics approval No ethics approval was required for this study. Contributors AA, conceptualization, data curation, formal analysis, investigation, visualization, writing - original draft preparation. NS-C, conceptualization, data curation, formal analysis, investigation, project administration, supervision, visualization, Writing – original draft preparation, Writing – Review & Editing, guarantor. GF, data curation, formal analysis, investigation. STB, data curation, formal analysis, investigation. RJS, supervision, Writing – Review & Editing. IS, conceptualization, resources, project administration, supervision, Writing – Review & Editing, LVS, conceptualization, project administration, supervision, Writing – Review & Editing. Competing interests .tere. The authors have no competing interest to declare. Data availability statement No additional data available. Funding None. 

451	Table 1. Mech Compound	anisms of action of all Mechanism of action
	Cimetidine	GSK3beta inhibition (88)
	Clozapine	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin(91)
	Haloperidol	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin(91)
	Lithium	GSK3beta inhibition(88)
	Olanzapine	GSK3beta inhibition(88)
	Valproic acid	GSK3beta inhibition(88)

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3 4 5	708 709		Case-control Study. Clin Psychopharmacol Neurosci [Internet]. 2022 Aug 1 [cited 2024 Dec 2];20(3):526–35. Available from: https://pubmed.ncbi.nlm.nih.gov/35879037/				
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	732 733 734 735	86.	Legge SE, Walters JT. Genetics of clozapine-associated neutropenia: recent advances, challenges and future perspective. https://doi.org/102217/pgs-2018-0188 [Internet]. 2019 Feb 15 [cited 2023 Nov 15];20(4):279–90. Available from: https://www.futuremedicine.com/doi/10.2217/pgs-2018-0188				
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52 53 54 55 56 57	743 744 745	89. Sutton LP, Honardoust D, Mouyal J, Rajakumar N, Rushlow WJ. Activation of canonical Wnt pathway by the antipsychotics haloperidol and clozapine involve					
58 59			Eer peer review enty, http://hmiepen.hmi.com/site/about/guidelines.yhtml				

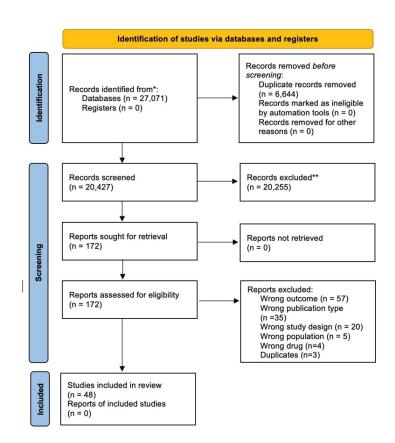
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canonical Wnt pathway by the antipsychotics haloperidol and clozapine involves dishevelled-3. J Neurochem [Internet]. 2007 Jul [cited 2021 Nov 30];102(1):153-69. Available from: https://pubmed.ncbi.nlm.nih.gov/17472703/

#### **FIGURE LEGEND**

Figure 1. Article selection flow diagram. The identification of studies via databases and registers is presented above. The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion. The protocol was performed based on the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

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### Table S1: The search strategy

1 2 3

Database	
PubMed	(Lithium[Title/Abstract] OR valpr*[Title/Abstract] OR tideglusib[Title/Abstract] OR AZD1080[Title/Abstract] OR FX322[Title/Abstract] OR Chir99021[Title/Abstract] OR TWS119[Title/Abstract] OR LY2090314[Title/Abstract] OR TDZD8[Title/Abstract] OR SB216763[Title/Abstract] OR CHIR98014[Title/Abstract] OR AR-A014418[Title/Abstract] OR Cimetidine[Title/Abstract] OR Olanzapine[Title/Abstract] OR 6-bromoindirubin-3'-oxime [Title/Abstract] OR Itle/Abstract] OR Clozapine [Title/Abstract] OR Haloperidol [Title/Abstract] OR Kenpaullone [Title/Abstract] OR L803mts [Title/Abstract] OR lthium[MeSH Terms] OR valproic acid[MeSH Terms] OR olanzapine[MeSH Terms] OR haloperidol[MeSH Terms] OR gsk3 inhib*[Title/Abstract] OR wnt acti*[Title/Abstract] OR wnt agon*[Title/Abstract] OR Beta catenin activ*[Title/Abstract]) AND ("Neoplasms"[Mesh] OR adenoma*[tw] OR anticarcinogen*[tw] OR blastoma*[tw] OR cancer*[tw] OR carcinogen*[tw] OR carcinom*[tw] OR hodgkin's disease[tw] OR hodgkins disease[tw] OR leukemi*[tw] OR melanom*[tw] OR lymphangioma*[tw] OR lymphangioma*[tw] OR melanom*[tw] OR melano
	OR teratocarcinoma*[tw] OR teratoma*[tw] OR tumor*[tw] OR tumour*[tw])
EMBASE	('lithium':ti,ab,kw OR 'valpr*':ti,ab,kw OR 'tideglusib':ti,ab,kw OR 'azd1080':ti,ab,kw OR 'fx322':ti,ab,kw OR 'chir99021':ti,ab,kw OR 'tws119':ti,ab,kw OR 'ly209314':ti,ab,kw OR 'tdzd8':ti,ab,kw OR 'sb216763':ti,ab,kw OR 'chir98014':ti,ab,kw OR 'ara014418':ti,ab,kw OR 'chir98014':ti,ab,kw OR 'olanzapine':ti,ab,kw OR 'chir98014':ti,ab,kw OR 'clozapine*':ti,ab,kw OR 'haloperidol':ti,ab,kw OR 'kenpaullone':ti,ab,kw OR 'l803mts':ti,ab,kw OR 'gsk3 inhib*':ti,ab,kw OR 'wnt acti*':ti,ab,kw OR 'wnt agon*':ti,ab,kw OR 'beta catenin activ':ti,ab,kw OR 'l803mts':ti,ab,kw OR 'yolaproic acid'/exp OR 'tideglusib'/exp OR 'haloperidol'/exp OR 'olanzapine'/exp OR 'neoplasm' OR adenoma*:ti,ab,kw OR anticarcinogen*:ti,ab,kw OR blastoma*:ti,ab,kw OR carccinogen*:ti,ab,kw OR carccinogen*:ti,ab,kw OR carcinosarcoma*:ti,ab,kw OR chordoma*:ti,ab,kw OR germinoma*:ti,ab,kw OR gonadoblastoma*:ti,ab,kw OR hepatoblastoma*:ti,ab,kw OR ((hodgkin* NEXT/1 disease):ti,ab,kw OR neuroma*:ti,ab,kw OR malignan*:ti,ab,kw OR neoplas*:ti,ab,kw OR neuroma*:ti,ab,kw OR neuroma*:ti,ab,
ochrane	(Lithium OR valpr* OR tideglusib OR AZD1080 OR FX322 OR Chir99021 OR TWS119 OR LY2090314 OR TDZD8 OR SB216763 OR CHIR98014 OR AR-A014418 OR Cimetidine OR Olanzapine OR Clozapine OR Haloperidol OR Kenpaullone OR L803mts OR gsk3 inhib*OR wnt acti*OR wnt agon*OR Beta catenin activ*)
	AND
	(adenoma* OR anticarcinogen* OR blastoma* OR cancer* OR carcinogen* OR carcinom* OR carcinosarcoma* OR chordoma* OR germinoma* OR gonadoblastoma* OR hepatoblastoma* OR (hodgkin* NEXT/1 disease) OR leukemi* OR lymphangioma* OR lymphangiomyoma* OR lymphangiosarcoma* OR lymphom* OR malignan* OR melanom* OR meningioma* OR mesenchymoma* OR mesonephroma* OR metasta* OR neoplas* OR neuroma* OR nsclc OR oncogen* OR oncolog* OR paraneoplastic OR plasmacytoma* OR precancerous OR sarcoma* OR teratocarcinoma* OR teratoma* OR tumor* OR tumour*)

### Page 27 of 42

			use	Control condition	group	Cancer risk Wnt group = prevalence	in Abbalysis (95%) Lucin 6	cancer prevalence	bias verdic
Chavez	2020	USA	Psychiatric	kaiser permanente consortium	92.6 per 100.000 person years	64 per 100.000 person years	ୁକ୍ର ମାନ ଥ୍ରୁପି.64 (0.51-0.79) <b>ଚ୍ଚିତ୍ର ଜୁନ୍ଦ୍ର</b>	No, decreased risk	Good
Lin	2018	Taiwan	Bipolar disorder	patients treated with anticonvulsants who did not use VPA	76/2663 (2.9%)	66/2663 (2.5%)	seignement Superation (0.563-1.277)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	ext and data	No	Good
Каае	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any ECC 1.3(1.1-1.4), CMM 1(0.8 ) MCC 1.2(0.2-8.7), SCC 3.3(1.1-1.6) Per 5 eas of use: BCC 1.1 (0.9- 1.4); MM 1 0.9 (0.5-1.5) MCC Nedata; SCC 0.8 (0.5-1.4)	No dose response	Good
Kang	2014	USA	Phsychiatric or neurologic disease	Smokers, never used VPA	9957/412717 (2.41%)	491/26911(2.58%)	لق ق lung ( 296 Head and neck (0.68), prostate (697), colon and rectum 10.99, bladder (0.93)	No	Good
Singh	2011	UK	Neurologic	Unexposed to VPA	4.56 (4.19–4.96) /1000 person years n= 551	5.11 (4.37–5.98)/1000 person years n=155	The second secon	No	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.8 <b>6</b> 7 (0.642-1.032)	No	Goo

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Fable S3. Data ex	traction an	d results tabl	le for non-coho	rt studies on the us	BMJ Օր se of VPA	ben	/bmjopen-2025-10; 1 by copyright, incl		Page 28 d
Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	ight, inclusti Analysi	Increase in cancer prevalence	Risk of bias verdict
George	2023	Sweden	Antiepileptic	Matched controls	766 without cancer and exposed to VPA / 156036	117 patients with cancer exposed to VPA /31474	명 for OR (95% 33) 0.85 (0.5% 35%) 0.85 (0.5% 35%) 2.5%	no	Good
Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	eignemene greene OR = 1.20 OR = 1.20 text text text text text text text tex	No	Good
Li	2024	Taiwan	Psychiatric	Matched controls	15540 matched controls	33 cases exposed (8.1%) 1438 cases unexposed (9.1%)	aded frog orieur (199-0.56) OR=0.58 minin	Decrease	Good
Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	1623 (0.2%)	162 (0.2%)	No Sprincant difference R not reported	No	Good
Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	Х	×	0.62 (@42-992) OR	Decrease	Good
Stritzelberger	2020	Germany	Neurologic	Epilepsy without cancer	21.0% of non cancer cases used VPA	21.5% of cancer cases used VPA	and <u>si</u> mil	No	Poor
Table	S4. Data ex	traction and		r cohort studies on		m mj.com/site/about/guidelii	0 p⊄on June 8, 2025 at Agence Bibliographique de l gimilar technologies.		

1	e 29 of 42				BMJ	Open	d by copyright,	Vbm jopen-2025-103496 c		
2 3 4 5	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt n group = u prevalence	40 Agnalysis (95%)	Increase in cancer prevalence	Risk of bias verdict
6 7 8 9	Asgari	2017	USA	Ever exposed	Kaiser permanente consortium	14008 (92.5 per 100,000 person years)	48 (67.4 per <b>9</b> 100,000 person <b>5</b> vears)	Anadjusted = 0.68 0.51-0.90); HR djusted: 0.77 0.58-102)	No, decrease	Good
10 11 12 13 14	Lin	2018	Taiwan	Bipolar disorder	Patients treated with anticonvulsants who did not use lithuim	48/1850 (2.6%)	26/925 (2.8%) 26/925 (2.8%)	<b>§</b> 1(0.6-1.6)	No	Good
15 16 17 18	Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	data 19/609 (3.12%) ata m Eg	e 1.19 (0.71-2.01)	No	Good.
19 20 21 22	George	2019	USA	Antiphysicotic medication	Postmenopausal women not treated with lithium	10079/155095 (6.5%)	ing, · 18/326 (5.5%) Al train	92 (0.58-1.46)	No	Good
23 24	Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	6 patients (1.6%) o	26 (0.186-0.975)	No, decrease	Good
25 26 27 28	Kessing	2015	Denmark	Psychiatric	Randomly selected sample from Danish population	Total amount of subjects: 24.272	(0.86%)	end test: HR = 1.01 (0.97-1.05)	No	Good
29 30 31 32 33	Kessing	2024	Denmark	Psychiatric	Lamotrigine use	Cohort 1: 4,281 (18.7%) Cohort 2: 71,069 (21.4%)	Cohort 1: 4,496 hoo (15.8%) Cohort 2: 13,422 <b>ge</b> (18.3%) s	Rsk difference= Cohort 1: -2.8% (- 2 9.7%; 4.1%) Cohort 2: -3.0% (- 2 6.0%; -0.1%)	No	Good
34 35 36 37	Martinsson	2016	Sweden	Psychiatric	General population compared to Bipolar disorder (with and without lithium)	166,443 (6.4%)		gence 04 (0.89-1.23)	No	Good
38 39	Zaidan	2014	France	Bipolar disorder	Matched ( EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	ograp p=0.04	Yes	Poor
40 <sup>∟</sup> 41 42 43 44 45 46				For	peer review only - http://bmjope	n.bmj.com/site/abou	ıt/guidelines.xhtml	bliographique de l		

a extract	ion and resu	BMJ Open and results table for case-control studies on the use of lithium						Page 30 of	
Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	بن Analysis (95%)	Increase in cancer	Risk of bias verdict	
2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	for 1.19 (1.03-1.35) 8 s	Yes, minimal (not all data shown, not the main question)	Poor	
2018	Israel	Bipolar disorder	All members if LHS (Health insurance company)	Expected cancer cases: 68	Expected cases Lithium group: 61.09	incidence ratio () 0.93(0.6-1.38); fenal 1.25 (0.91-1.6)	No	Poor	
2024	Taiwan	Psychiatric	Matched controls	15,540 matched controls	45 cases exposed (9.1%) 1470 cases unexposed (9.1%)	and:		Good	
2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	1.01(0.86-1.15)	No	Good	
2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	ų,	No	Good	
2008	Canada	Psychiatric	No history of cancer	257 (0.8%)	69 (0.9%);	difference <u>ø</u>	No No	Poor	
			For poor roview only b	ttp://bmiopop.hmi	com/sito/about	hnologies.	8 2025 at Anence Ribliographicup		
	Year 2009 2018 2024 2016a 2016b	YearLocation2009Denmark2018Israel2024Taiwan2016aDenmark2016bDenmark	YearLocationIndication for use2009DenmarkAny use2018IsraelBipolar disorder2024TaiwanPsychiatric2016aDenmarkAny use2016bDenmarkAny use	YearLocationIndication for useControl condition2009DenmarkAny useMatched (age/sex) controls2018IsraelBipolar disorderAll members if LHS (Health insurance company)2024TaiwanPsychiatricMatched controls2016aDenmarkAny useMatched (age/sex) controls2016bDenmarkAny useMatched (age/sex) controls2008CanadaPsychiatricNo history of cancer	YearLocationIndication for useControl conditionCancer risk Controls: 260 exposed, 595256 unexposed2009DenmarkAny useMatched (age/sex) controlsControls: 260 exposed, 595256 unexposed2018IsraelBipolar disorderAll members if LHS (Health insurance company)Expected cancer cases: 682024TaiwanPsychiatricMatched controls15,540 matched controls2016aDenmarkAny useMatched (age/sex) controlsNot reported 6453/257978 (2.5%)2008CanadaPsychiatricNo history of cancer257 (0.8%)	YearLocationIndication for useControl conditionCancer risk Controls group prevalence Controls: 260Cancer risk prevalence Controls: 260Cancer risk prevalence2009DenmarkAny useMatched (age/sex) controlsControls: 260 exposed, s95256 unexposed779/5953972018IsraelBipolar disorderAll members if LHS (Health insurance company)Expected cancer cases: 68Expected cases Lithium group: 61.092024TaiwanPsychiatricMatched controls15,540 matched (9.1%)45 cases exposed (9.1%)2016aDenmarkAny useMatched (age/sex) controlsNot reported 6453/257978 (2.5%)159/15712016bDenmarkAny useMatched (age/sex) controlsNot reported 6453/257978 (2.5%)19/15712008CanadaPsychiatricNo history of cancer257 (0.8%)69 (0.9%);	YearLocationIndication for useControl conditionCancer risk Control group prevalenceCancer risk prevalenceAnalysis (95%)2009DenmarkAny useMatched (age/sex) controlsControls: 260 exposed, 595256 unexposed779/5953971.19 (1.03-1.5m ref2018IsraelBipolar disorderAll members if LHS (Health insurance company)Expected cancer cases: 68Traiwan (9.1%)Standardize ratio (9.1%)2024TaiwanPsychiatricMatched (age/sex) controls15,540 matched (9.1%)45 cases (9.1%)OR = 0.81 (0.9%) (9.1%)2016aDenmarkAny useMatched (age/sex) controlsNot reported (2.5%)159/15711.01(0.86-1.15) (0.1%)2016bDenmarkAny useMatched (age/sex) controlsNot reported (2.5%)159/15711.01(0.86-1.15) (0.1%)2018CanadaPsychiatricNo history of cancer257 (0.8%)69 (0.9%);No significare (0.1%);2008CanadaPsychiatricNo history of cancer257 (0.8%)69 (0.9%);No significare (0.1%);	Year         Location         Indication for use         Control condition         Cancer risk Controls: 260         Cancer risk Wnt group         Analysis (95)         Increase in cancer prevalence           2009         Denmark         Any use         Matched (age/sex) controls         Control: 260 (spi226)         779/595397         1.9 (1.0.1.3)         Termark         Yes, minimal (not all data shown, not the main question)           2018         Israel         Bipolar disorder         All members if LHS (Health insurance company)         Expected cancer cases: 68         Expected (9.1%)         Standardize (scases)         Standardize (scases)         No           2016a         Denmark         Any use         Matched (age/sex) controls         Not reported (9.1%)         10/10.08-1.1%)         No           2016a         Denmark         Any use         Matched (age/sex) controls         Not reported (2.5%)         13/9/1571         1.01(0.86-1.1%)         No           2016a         Denmark         Any use         Matched (age/sex) controls         Not reported (2.5%)         13/9/1571         1.01(0.86-1.1%)         No           2016a         Denmark         Any use         Matched (age/sex) controls         6453/257978         14/461 (3.0%)         OR = 1.3 (0.7 £3)         No           2008         Canada         Psychiatric         No	

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## BMJ Open

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2 3 4	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Lincrease in Concer Concer Concer Concer	Exposure duration	Risk of bias verdict
5 6	Moller	1989	Denmark	Gastro- intestinal	No control, na	tional incidence		RR= 1.5 (p<0.001)	6 of es	not specified	Poor
7 8 9 10	Rossing	2000	USA, western Washington State	Gastro- intestinal	All males/females in the area	Total cohort = 48.512 users. Cases not shown	267 cimetidine Cases	0.9 (0.8–1.1)	0 May <sup>2</sup> 2025. Enseigne uses relate	not specified	Good, however not all data shown.
11 12 13 14	Velicer	2006	USA	Gastro- intestinal	Victims and lifestyle cohort	478 (1.8%) (incidence=7.6)	20 (1.6%)(incidence is 8.5)	RR= 0.97 (0.61- 1.53)	Downloade ment Super d to text an	not specified	Fair
$\begin{array}{c} 15 \\ 16 \\ 17 \\ 18 \\ 19 \\ 20 \\ 21 \\ 22 \\ 23 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 31 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ 37 \\ 38 \\ 39 \\ 40 \\ 41 \\ 42 \\ 43 \\ 44 \\ 45 \end{array}$							open.bmj.com/site/ak		2025 at Agence Bibliographique de ologies.		

ble S7. Data ext	raction and res	ults tab	le for surve	illance and c	case-control	BMJ Open studies for the us		/bmjopen-2025-103296 o d by copyright, including		Page 32 of
Type of study	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence		Increase in cancer prevalence	Risk of bias verdict
Connecillare	Colin jones	1991	UK	Gastro- intestinal	x	x	111/9928 (1.1%)		No	Poor
Surveillance	Colin jones	1985	UK	Gastro- intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	ay 202 reigr	No	N/A
	Coogan	2005	USA	Gastro- intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	1000 = 0.9 (0.6-1.2)	No	Poor
	Holly	1997	USA	Gastro- intestinal	Never use	Х	X	for uses reigned to text and data to text and text	Decrease	Poor
Case-control	Mathes	2008	USA	Gastro- intestinal	Never users	n= 1390, 1136 (92.5%) unexposed; 92 5(7.5%) ever use; 36 (2.9%) > 2 years	Ductal carcinoma: n=1148; 939 (92.1%) never use; 81 (7.9%) ever use; 27 (2.6%)>2 years of use	Ever use 1.5); Log ulas carcinoma OR = 1.1 (0.8- 1.5); Log ulas carcinoma OR = 1.0 (0.7- 1.6); >2 pears use ductal carcinoma, 0.9 (0.5-1.5); tob gar carcinoma, 1.1(0.6-1.9)	No	Good
	Moller	1992	Denmark	Gastro- intestinal		l controls Group tional pharmacy	191	QR = 2.1 (0.7-6.3)	No	Poor
	Schumacher	1990	USA	gastro- intestinal	Non users	x	x	Ope = 251 (95% CI = 0.7-6.3)	No	Poor
							com/site/about/guide	Omilar technologies.		

ge 33 of 42 Table S8. Data	a extraction	and results t	able for cohort s	tudies on the use		l Open clozapine, and olanzapi	/bmjopen-ź J by copyri ne		
Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	vbmjopen-2025-10329، on d by copyright, including f Analysis Analysis	Increase in cancer prevalence	Risk bias verdi
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	97 30 HR = 1.05 50 A 24 1.21 5 8 7 8 24	No	Goo
Tiihonen	2022	Finland	Clozapine (schizophrenia)	matched controls (schizophrenia patient without cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted O	Yes, hematologic	Goo
							from http:// ur (ABES) - data mining		
							http://bmjopen.bmj.com/ on June 8, 2025 at ES) . nining, Al training, and similar technologies.		
							mjopen.bmj.com/ on June 8, 2025 at Al training, and similar technologies.		
							ne 8, 2025 a echnologie:		
							· >		
							gence Bibliographique de l		
			F	or peer review only	y - http://bmjope	n.bmj.com/site/about/gu	idelines.xhtml		

Study	Year	Location	Drug of interest	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	/bmjopen-2025%03296 d by copyright, 前95%03296 Analysiscludir	Increase in cancer prevalence	Risk o bias verdio
Brainerd	2024	USA	Clozapine	Matched controls	23,043 (4.1%)	2,306(5.3%)	OR = 1.31 (608-4.60		Good
		_	Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% CD is සි75 (1.31–ද්දීණු සි	yes	
Chen	2022	Taiwan	Olanzapine	Matched controls	63/37908	13/9502	OR (95% ເມື່ອ)22 (0.38− <b>11</b> 55)	no	Goo
			Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% இறி 14 (0.56– <b>க் ஆழ</b>	no	
	2020			Not treated with	39553/1962602 (2.0%)	4/352 (1.1%)	ତନ = 0.54 (୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦୦		
Friedman	2020	USA	Haloperidol	haloperidol	576	4/576 (0.7%)	OR = 0.32 (0.1 1 1		Goo
			Clozapine	Non-gastric cancer	2008 92 (0.06%)	30/2008 (1.5%) 4 (0.01%)	OR = 0.69 (Cata do .99 OR = 0.35 (Cata do .99 OR = 0.35 (Cata do .99)		
Hsieh	2019	Taiwan	Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (0-14-9.46	) No, decrease	N/A
		_	Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (505 3).3	5) No, decrease	_
Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted Of 1:3:30 (1.09-1656) Adjusted Of 2: 5:15 (0.9-1377) 2	model (2), yes when	Goo
Tiihonen	2022	Finland	Clozapine	No cancer	3734 matched controls (9.9used clozapine%)	375 cases; 19,5% used clozapine.	aOR = 2.94 (1700 - 2007	7) Yes, hematologic cancers	Goo
				For peer review c			gence Bibliographique de		

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ge 35 of 42 Table S10. Data extraction and results table for pharmacovigilance and database studies on the use of haloperidol, clozapine, and olanzapine

Szarfman	2019	Clozapine Haloperidol Olanzapine Clozapine	x x	Pituary tumor Pituary tumor	17 cases	igi -20 2025 in Abalysis (95%) udi 229 in RR <sup>6</sup> 0.98 (0.5-1.8)	No	
Szarfman		Olanzapine		Pituary tumor				
	2006			r ituary turnor	11 cases	₫ RR = 7.0(4.35-11.3)	Possibly	N/A
	2006	Clozanino	х	Pituary tumor	17 cases	<b>ឆ្</b> ̄ Rm <b>- 2</b> .53 (1.57-4.1)	Possibly	
	2006	Ciuzapine	x	Pituary tumor	4 cases	0.9 (0.4-1.7)	No	
Chretien		Haloperidol	x	Pituary tumor	9 cases	a / R K = 5.6 (2.9-13)	Possibly	N/A
Chretien		Olanzapine	x	Pituary tumor	11 cases	2.3 (1.4-3.7)	Possibly	
Chretien	2024	Clozapine	x	Hematologic malignancies	275	aR	Possibly	
	2021 –	Olanzapine	x	Hematologic malignancies	68	aR 20.88 (0.66- 1.16)	No	N/A
Maeshima	2021 -	Haloperidol	x	Benign and malignant breast cancer	939	፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲ ፲	No	N/A
Waeshina	2021	Olanzapine	x	Benign and malignant breast cancer	1825	29991 (0.07, 3.51) ROR	No	N/A
Dawson	2023	Clozapine	x	Hematological	104/384	excess af .he matological cancers in people expozed to clozapine	<sup>1</sup> Possibly	
				Neoplasm	61/384	jope I trai	No	
				Lung	50*384	inir en.t	No	
				Breast	37/384	ng, a	No	
				Colorectal	28/384	open.bmj.com/ on June 8, 2025 at training, and similar technologies	No	
				Brain	18/384	sim o	No	
				Skin	17/384	on June milar tec	No	
				Esophagogastric	11/384	une .	No	N/A
				Pancreatic	10/384	chn 8,	No	
				Urological	9/384	2025 Dologi	No	
				Testicular	8/384	gies	No	
				Hepatic	7/384	 Ag	No	
				ENT	6/384	at Agence es.	No	
				Gynecological	<5/384	ë	No	
				others	14/384	Biblio	No	
Uwai	2024	Clozapine	х	All non-hematologic malignancies	1668	Reporting Odds Ratio= 1.28	Possibly	N/A

#### Table S11. Critical appraisal table for cohort studies on the use of VPA

bla 611 (			for ook out at u	ice on the use of VDA		J Open	/bmjope d by cop			F	Page 36 of
DIE 311. (		appraisai table	for conort stud	ies on the use of VPA			/bmjopen-2025-103296 on ع d by copyright, includin lilitor compari <b>t</b> a fts - Compari <b>ta</b>				
					Selection max 1 star)		03296 ncludir	( (n	Dutcome nax 1 star)		
Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	<ul> <li>Comparibility on 30 May 2025. Do (max 2 starseigneme)</li> <li>(max 2 starseigneme)</li> <li>** elated t</li> </ul>	Ascertainment of outcome	Long enough follow up	Adequace of follow up	Verdict
Chavez	2020	Retrospective cohort		*	*	*	ignem elated *	*	*		Good
Lin	2018	retrospective cohort study	*	*	*	*	. Downloaded ( ment Superieu ed to text and c * * *	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	uperieu t and *	*	*	*	Good
Каае	2010	population- based cohort study	*	*	*	*	from htt ur (ABES data min * *	*	*	*	Good
Kang	2014	retrospective cohort study		*	*	*	ing, A **	*	*	*	Good
Singh	2011	cohort study	*	*	*	*	l from http://bmjopen.bmj.com/ ur (ABES) . data mining, Al training, and si * * * * * * *	*	*	*	Good
Yang	2022	Nationwide cohort	*	*	*		and si **si	*	*	*	Good
						C	on June 8, 2025 at Ay milar technologies.				
				For peer review o	nly - http://hmione	n.bmj.com/site/about/guide	gence Bibliographique de I				

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5	37 of 42				4h aa		MJ Open		/bmjopen-2028 4 by convright			
1 2	able S12. Critica	a apprais	sal table for case	control studies on	Selectior (max 1 sta	ı	Compai (max 2		Y'			
3 4 5 6 7 8	Author	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	Comparability cases and	off 36 May Ensi	certain nent of utcome	Non- response rate	Verdict
9 10	George	2023	case-control	*	*	*	*	**	2025. eignei relate	*	*	Good
11 12	Hallas	2009	case control	*	*	*	*	** 6			*	Good
13 14	Li	2024	Nested Case control	*	*	*	*	**	vnloac Supe	*	*	Good
15 16	Kristensen	2019	nested case control	*	*	*	*	* 0	Downloaded from http://bmjope nent Superieur (ABES) . d to text and data mining. Al train	*	*	Good
17 18	Salminen	2016	case-control	*	*	*	*	**	a min	*	*	Good
19 20	Stritzelberger	2020	Nested case control	N/A High ri	sk of bias, no	ot the aim of the	e study and not all data sho	own 🦉	) ) ) )	1		Poor
21 22	Tilhonen	2022	case-control	*	*	*	*	**	joper I trair	*	*	Good
<ol> <li>23</li> <li>24</li> <li>25</li> <li>26</li> <li>27</li> <li>28</li> <li>29</li> <li>30</li> <li>31</li> <li>32</li> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> </ol>				For per	er review on	ıly - http://bmjo	pen.bmj.com/site/about/g		mjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Al training, and similar technologies			

					Selection nax 1 star)		d by copyright, includi	/bmjopen-2025-103296	Outcome (max 1 sta		
Author	Year	Type of study	Representatitveness of cohort	Selection of non- exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparibility of cohorts of (max 2 stars)	Ascertain Ascertain Thent of Soutcome	Long enough follow up	Adequace of follow up	Verdict
Asgari	2017	retrospectiv e cohort		*	*	*	tement s	25. Dowr	*	*	Good
Lin	2018	retrospectiv e cohort study	*	*	*	*	s related to text and d * * *	* *	*		Good
Cohen	1998		*	*	*	*	ata n **		*	*	Good
George	2019	restrospectiv e cohort study	*	*	*	*	nining, Al **	* http://bmj	*		Good
Huang	2016	retrospectiv e cohort study	*	*	*	*	ur (ABES) . data mining, Al training, and similar techr * * * * * * * * * *	jopen.bmj	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	and simila *	.com/ on c	*		Good
Kessing	2024	Cohort (Population based)	*	*	*	*	ar technologies. * * *		*	*	Good
<b>A</b> artinsson	2016	Cohort nationwide		*	*	*	ogies.	* 2025 at A	*	*	Good
Zaidan	2014	retrospective cohort study	N/A - Data from coho	ort compar	ed to general po	opulation, expressed a	is standardized inci	genceatio gencebibliographique de l	; small cohor	t	Poor

AuthorYearType of study Adequact definHallas2009case controlKahan2018study from large database		s Selection of	Definition of controls	Comparability of cases and	no n	ain Non- of response me rate	Verdic
Kahan2009Case-controlKahan2018study from	*			(	nt or		
Kahan 2018 study from			*		* Noad Super	*	Poor
	Da	ata from large dat	* tabase, scale non-applicabl * * *	e, high risk of bia	ed from h ieur (ABE		Poor
Li 2024 Nested Case <b>*</b> control	: *	*	*	** "	* ttp://bn IS) . Ining, /	*	Good
Nationwide Pottengard 2016 (1) case control <b>*</b> study	• *	*	*	**	* njopen.b	*	Poor
Case control Pottengard 2016 (2) study * nationwide	: *	*	*	**	mj.com/ a. and si	*	Good
Tamim 2008 Nested case- control	* *	*	*	** Lithium not main question of study	* on June 8, 2025 at . milar technologies.	*	Poor

le S15. Criti	ical appra	isal table for co	phort studies on the us	ise of cime		ИJ Open	(7 	/bmjopen-2025-103296 / by copyright, includi <del>t</del>			Page 40
				Select	tion (max 1 star)			025-10329 3ht, includ	Outcome (max	( 1 star)	
Author	Year	Type of study	Representatitvenes s of cohort	Selection of non- exposed cohort	Ascertainment	Demonstration that outcome of interest was not present at start of study	Comparability a cohorts (max 2 stars)	Asscertain Bent of	Long enough follow up	Adequace of follow up	Verdict
Moller	1989	Cohort	No control, high risk o	of bias				125. Dov Inemen			Poor
Rossing	2000	Retrospective cohort study	•	*		*	**	* wnload It Super	*	*	Good
Velicer	2006	Cohort study		*		*	**	* ed fro rieur (	*	*	Fair
						*		weight we			
								hique			

age 41 of 42 Table S16. (	Critical a	appraisal	table for surveil	lance and case-co	ontrol stud		MJ Open of cimetidine	Comparibilit	d by copyright, inclu			
						Selection (max 1 star)		Comparibilit (Max 2 stars	ght, inclu			
Auth	hor	Year	Type of study	Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	(Max 2 stars Comparability cases and controls	∰or uses relation	scertain hent of utcome	Non- response rate	Verdict
Colin J	lones	1985	case control study	No representative	e outcome;	already had gas	trcic ulcers, only age and s	ex matched cor	1em@nt			Poor
Colin J	lones	1991	surveillance study	No control, N/A					Supe			N/A
5 5 Coog	gan	2005	Database study/case- control	*		*		**	rieur (AB nd data n	from		Poor
Hol	lly	1997	population- based case- control study				*	**	ES) . nining, A	*		Poor
Matl	hes	2008	Population based case- control study	*	*	*	*	**	I training	*		Good
Mol	ller	1992	Case-control study	High risk of bias			trcic ulcers, only age and s * *		, and simil			Poor
Schum	acher	1990	Case-control study	*	*			**	ar techr	8		Poor
									נ	₽ >		
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				For pee	er review on	ily - http://bmjo	pen.bmj.com/site/about/	guidelines.xhtn	าเ			

Table S17.	Critical	appraisal table	for cohort stu	dies on the use of hal		J Open e, and olanzapine	/bmjopen-2025-103296 on 1 by copyright, includin <b>ig</b> ft comparies the second se			
					Selection		includi	(	Dutcome	
Author	Year	Type of study	Representa titveness of cohort	Selection of non- exposed cohort	(max 1 star) Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	- Comparidiality of coho安ts 30 (max 2 s歸所為 s 5 5 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7	Accortainmont	nax 1 star) Long enough follow up	Adequace of follow up
Tilhonen	2022	cohort study	*	*	*	**	2025. elate *	*	*	
Wang	2002	Retrospective cohort	*		*	*		*	*	*
						*	3, 2025 at Agence Bibliographique de Inologies.			

Verdict

Good

Good

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Author	Year	Type of study	Selection (max 1 star)				e Comparibil (max 2 sta		Vomiopen-2025- 10325- 10322 (max 1 star)		
			Adequacy of case definition	Represent ativeness of the cases	Selection of controls	Definition of controls	Comparibility of	lg for∺u	g Scertain	Non- response rate	Verdict
Brainerd	2024	Case Control study	*	*	*	*	**	nent Su d to tex	*	*	Good
Chen	2022	Case-control study	*	*	*	*	**	perieur t and d	*	*	Good
Friedman	2020	Case-control	*	*	*	*	* *	(ABES ata min	om *	*	Good
Hsieh	2005	Database study/case- control		) . ing, <b>A</b> l tra	o://bmiop		Poor; N,				
Pottengard	1997	population- based case- control study	*	*	*	licable due to study desig	**	aining, ar	en.bmi.c	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	nd similar	* *	*	Good
								technologies.	ent of without of the second s		
									gence Bibliographique de l		