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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 17th 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.

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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

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

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Word count: 4497

Introduction

The Wnt/β-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/β-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/β-catenin signaling (Steinhart and Angers 2018). 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 (Kahn 2014; Berwick and Harvey 2012; 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/β-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 Wnt 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**

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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 17th, 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.

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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 case-control 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.

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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

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(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

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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

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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 17th, 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.

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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.

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Conflicts of Interests

The authors declare no conflicts of interest

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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.1471-4159.2007.04527.x
Haloperidol	Wnt 5 a, dishevveled-3, axin, gsk3 and beta catenin	https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1471-4159.2007.04527.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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Appendix: Compounds in search string.

AR-A014418

AZD-1080

Chir-99021

CHIR98014

Cimetidine

FX-322

Gemifloxacin

Hydroxychloroquine

Lithium

LY2090314

Olanzapine

SB216763

TDZD8

Tideglusib

TWS119

TWS119

Valproic acid

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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	Analysis (95%)	Increase in cancer prevalence	Exposure duration	Risk of bias verdict
Chavez	2020	USA	Psychiatric	kaiser permanente consortium	92.6 per 100.000 person years	64 per 100.000 person years	HR = 0.64 (0.51-0.79)	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%)	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%	0.848 (0.563-1.277)	No	cDDD (communitive daily dose of up to 215 days	Good
Kaae	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any use: BCC 1.3(1.1-1.5), CMM 1(0.8-1.3), MCC 1.2(0.2-8.7), SCC 1.3(1.1-1.6) Per 5 years of use: BCC 1.1 (0.9-1.4); CMM 1.09 (0.85-1.5) MCC *No data*, SCC 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 and neck (0.68), prostate (0.97), colon and rectum (0.9), bladder (0.93)	No	>1 year (<1 year excluded)	Good
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	Rate ratio = 1.18 (0.96–1.46)	No	>5 years, subgroup	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.877 (0.642-1.032)	No	>180 days	Good

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Table 3. Data extraction and results table for non-cohort studies on the use of VPA

Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	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	OR (95% CI) 0.85 (0.70-1.04)	no	Good
Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	OR = 1.21 (0.95-1.56)	No	Good
Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	X	X	OR of VPA not shown	No	Good article, however, not all data on VPA available
Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	X	X	0.62 (0.42-0.92) 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	p=0.760	No	Poor

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Table 4. Data extraction and results table for cohort studies on the use of lithium

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Exposure duration	Risk of bias 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)	No, decrease	<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)		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)		37% treated for > 5 years; 26.4% treated <2 years	Fair - good methodology, groups too 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)	No	! - 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)	No, decrease	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)	No	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)	No	unclear, 'high'	Good
Zaidan	2014	France	Bipolar disorder	Matched (EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	p=0.04	Yes	>20 years lithium exposure	Poor

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

Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Hallas	2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	1.19 (1.03-1.37)	Yes, minimal (not all data shown, not the main question)	Poor
Kahan	2018	Israel	Bipolar disorder	All members if LHS (Health insurance company)	Expected cancer cases: 68	Expected cases Lithium group: 61.09	standardized incidence ratio m 0.93(0.6-1.38); fe 1.25 (0.91-1.6	No	Poor
Pottengard	2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	1.01(0.86-1.1	No	Good
Pottengard	2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	OR = 1.3 (0.7-1	No	Good
Tamim	2008	Canada	Psychiatric	No history of cancer	69 cases lithium (0.9%); and 257 controls on lithium (0.8%)	-	N.A.	No	Poor

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Table 6. Data extraction and results table for cohort studies on the use of cimetidine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Exposure duration	Risk of bias verdict
Moller	1989	Denmark	Gastro-intestinal	No control, national incidence			RR= 1.5 (p<0.001)	Yes	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)	No	not specified	Good, however not all data shown.
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)	No	not specified	Fair

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Table 7. Data extraction and results table for surveillance and case-control studies for the use of cimetidine

Type of study	Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Surveillance	Colin jones	1991	UK	Gastro-intestinal	x	x	111/9928 (1.1%)	NO control group!	No	Poor
	Colin jones	1985	UK	Gastro-intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	not done	No	N/A
Case-control	Coogan	2005	USA	Gastro-intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	OR=0.9 (0.6-1.2)	No	Poor
	Holly	1997	USA	Gastro-intestinal	Never use	X	X	OR 0.39 (0.17-0.89)	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: Ductal carcinoma:OR= 1.1 (0.8-1.5); Lobular carcinoma OR = 1.0 (0.7-1.6); >2 years use ductal carcinoma, 0.9 (0.5-1.5) lobular carcinoma, 1.1(0.6-1.9)	No	Fair
	Moller	1992	Denmark	Gastro-intestinal	Matched controls Group health national pharmacy			OR = 2.1 (0.7-6.3)	No	Poor
	Schumacher	1990	USA	gastro-intestinal	Non users	x	x	OR = 2.1 (95% CI = 0.7-6.3)	No	Poor

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Table 8. Data extraction and results table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	HR = 1.05 (0.9 1.21)	No	Good
Tiihonen	2022	Finland	Clozapine (schizofrenia)	matched controls (schizofrenia patient withot cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted OR 3.5 (2.22-5.05) >5000 defined daily dose cumulative exposure	Yes, hematologic	Good

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Table 9. Data extraction and results table for case-control studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Drug of interest	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95% CI)	Increase in cancer prevalence	Risk of bias verdict
Chen	2022	Taiwan	Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% CI is 1.75 (1.31–2.34)	yes	Good
			Olanzapine	Matched controls	63/37908	13/9502	OR (95% CI) 0.82 (0.38–1.75)	no	
			Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% CI 1.14 (0.56–2.32)	no	
Friedman	2020	USA	Haloperidol	Not treated with haloperidol	39553/1962602 (2.0%)	4/352 (1.1%)	OR = 0.54 (0.20–1.44)	No	Good
					576	4/576 (0.7%)	OR = 0.32 (0.12–0.84)	No, decrease	
					2008	30/2008 (1.5%)	OR = 0.69 (0.48–0.99)	No, decrease	
Hsieh	2019	Taiwan	Clozapine	Non-gastric cancer	92 (0.06%)	4 (0.01%)	OR = 0.35 (0.13–0.97)	No, decrease	N/A
			Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (0.13–0.46)	No, decrease	
			Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (0.05–0.35)	No, decrease	
Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted OR 1:1.30 (1.09-1.56) Adjusted OR 2:1.15 (0.9-1.47)	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 (2.07–4.17)	Yes, hematologic cancers	Good

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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	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Lertxundi	2019	Clozapine	x	Pituary tumor	17 cases	PRR 0.98 (0.5-1.8)	No	N/A
		Haloperidol	x	Pituary tumor	11 cases	PRR 7.0(4.35-11.3)	Possibly	
		Olanzapine	x	Pituary tumor	17 cases	PRR 2.53 (1.57-4.1)	Possibly	
Szarfman	2006	Clozapine	x	Pituary tumor	4 cases	ROR 0.9 (0.4-1.7)	No	N/A
		Haloperidol	x	Pituary tumor	9 cases	ROR 5.6 (2.9-13)	Possibly	
		Olanzapine	x	Pituary tumor	11 cases	ROR 2.3 (1.4-3.7)	Possibly	
Chretien	2021	Clozapine	x	Hematologic malignancies	275	aROR 9.14 (7.75-10.77)	Possibly	N/A
		Olanzapine	x	Hematologic malignancies	68	aROR 0.88 (0.66- 1.16)	No	
Maeshima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1.03 (0.07, 3.51) ROR	No	N/A
		Olanzapine	x	Benign and malignant breast cancer	1825	2.03 (0.07, 3.51) ROR	No	
Dawson	2023	Clozapine	x	Hematological	104/384	excess of hematological cancers in people exposed to clozapine	Possibly	N/A
				Neoplasm	61/384		No	
				Lung	50*384		No	
				Breast	37/384		No	
				Colorectal	28/384		No	
				Brain	18/384		No	
				Skin	17/384		No	
				Esophagogastric	11/384		No	
				Pancreatic	10/384		No	
				Urological	9/384		No	
				Testicular	8/384		No	
				Hepatic	7/384		No	
				ENT	6/384		No	
				Gynecological	<5/384		No	
				others	14/384		No	

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

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Chavez	2020	Retrospective cohort		*	*	*	**	*	*		Good
Chia lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kaae	2010	population-based cohort study	*	*	*	*	**	*	*	*	Good
Kang	2014	retrospective cohort study		*	*	*	**	*	*	*	Good
Singh	2011	cohort study	*	*	*	*	**	*	*	*	Good
Yang	2022	Nationwide cohort	*	*	*		**	*	*	*	Good

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Table 12. Critical appraisal table for case control studies on the use of VPA

Author	Year	Type of study	Selection (max 1 star)				Comparibility of Cases abd controls (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
George	2023	case-control study	*	*	*	**	**	*	*		Good
Hallas	2009	case control	*	*	*	*	**	*	*		Good
Kristensen	2019	nested case control study	*	*	*	**	*	*	*		Good, however not all data available
Salminen	2016	case-control study	*	*	*	**	**	*	*		Good
Stritzelberger	2020	Nested case control (from cohort?)	High risk of bias, not the aim of the study and not all data shown								Poor
Tilhonen	2022	case-control study	*	*	*	*	**	*	*		Good

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Table 13. Critical appraisal table for cohort studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star)				Comparibility of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Asgari	2017	retrospective cohort		*	*	*	**	*	*	*	Good
Chia lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
George	2019	restrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	**	*	*		Good
Martinsson	2016	Cohort nationwide		*	*	*	**	*	*	*	Good
Zaidan	2014	retrospective cohort study	Non applicable - Data from cohort compared to general population, expressed as standardized incidence ratio; small cohort								Poor

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Table 14. Critical appraisal table for case-control studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star)			Comparability (max 2 stars)		Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Hallas	2009	case control	*	*	*	*	**	*	*	Good for VPA, bad for lithium
Kahan	2018	Case-control study from large database	Data from large database, scale non-applicable, high risk of bias							Poor
Pottengard	2016 (1)	Nationwide case control study	*	*	*	*	**	*	*	Poor
Pottengard	2016 (2)	Case control study nationwide	*	*	*	*	**	*	*	Good
Tamim	2008	Nested case-control	*	*	*	*		*	*	Poor

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Table 15. Critical appraisal table for cohort studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Moller	1989	Cohort	No control, high risk of bias								Poor
Rossing	2000	Retrospective cohort study	*	*		*	**	*	*	*	Good
Velicer	2006	Cohort study		*		*	**	*	*	*	Fair

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Table 16. Critical appraisal table for surveillance and case-control studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)			Comparibility (max 2 stars)		Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Colin Jones	1985	case control study	No representative outcome; already had gastrcic ulcers, only age and sex matched controls							Poor
Colin Jones	1991	surveillance study	No control, NA							N/A
Coogan	2005	Database study/case-control	*		*		**	Too short		Poor
Holly	1997	population-based case-control study				*	**	*		Poor
Moller	1992	Case-control study								Poor
Schumacher	1990	Case-control study	*	*			**			Moderate risk of bias?

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Table 17. Critical appraisal table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Tilhonen	2022	cohort study	*	*	*	**	*	*	*		Good
Wang	2002	Retrospective cohort	*	-	*	*	-	*	*	*	Good

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

Author	Year	Type of study	Selection (max 1 star)			Comparibility (max 2 stars)		Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparibility of cases and controls	Ascertainment of outcome	Non-response rate	
Chen	2022	Case-control study	*	*	*	*	**	*	*	Good
Friedman	2020	Case-control	*	*	*	*	**	*	*	Good
Hsieh	2005	Database study/case-control								Poor
Pottengard	1997	population-based case-control study	*	*	*	*	**	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	*	*	Good

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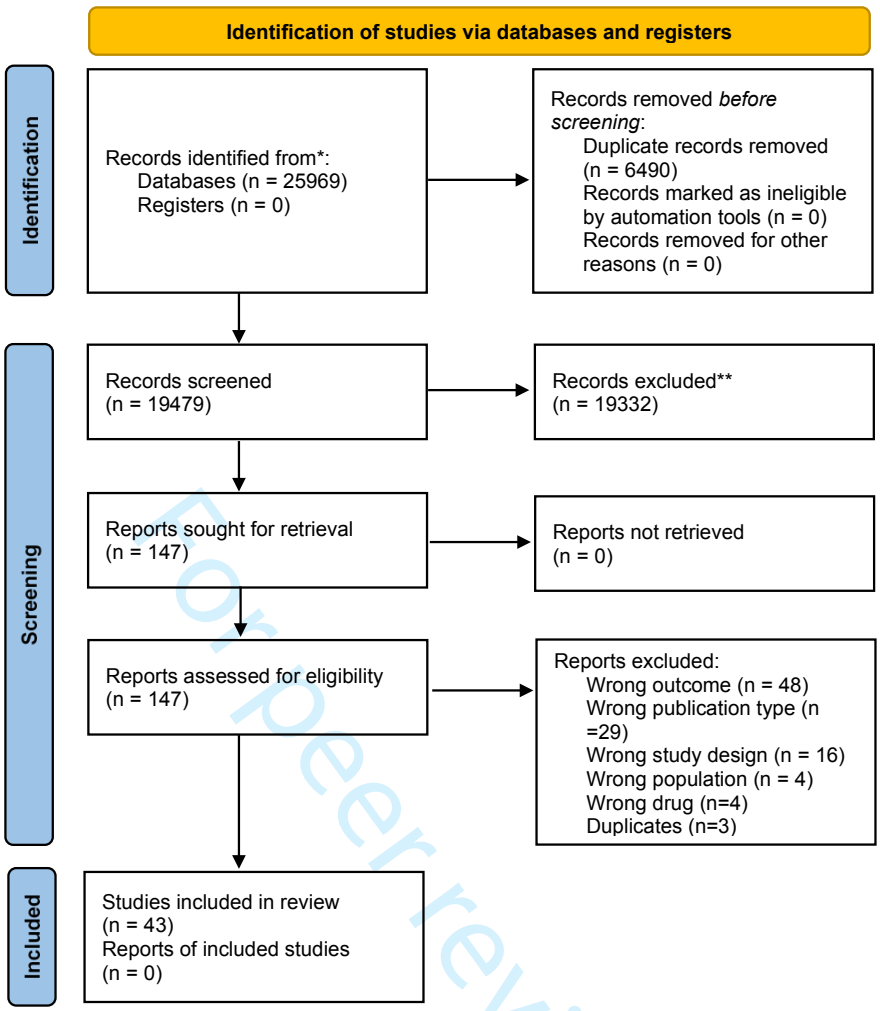

Figure 1: Article selection flow diagram. The identification of studies via databases and registers is presented above. The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion. The protocol was perfomed based on the PRISMA 2020 flow diagram 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] 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 Clozapine [Title/Abstract] OR Haloperidol [Title/Abstract] OR Kenpaullone [Title/Abstract] OR L803mts [Title/Abstract] OR lithium[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 carcinosarcoma*[tw] OR chordoma*[tw] OR germinoma*[tw] OR gonadoblastoma*[tw] OR hepatoblastoma*[tw] OR hodgkin disease[tw] OR hodgkin's disease[tw] OR hodgkins disease[tw] OR leukemi*[tw] OR lymphangioma*[tw] OR lymphangiomyoma*[tw] OR lymphangiosarcoma*[tw] OR lymphom*[tw] OR malignan*[tw] OR melanom*[tw] OR meningioma*[tw] OR mesenchymoma*[tw] OR mesonephroma*[tw] OR metasta*[tw] OR neoplas*[tw] OR neuroma*[tw] OR nsclc[tw] OR oncogen*[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 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 'cimetidine':ti,ab,kw OR 'olanzapine':ti,ab,kw OR '6-bromoindirubin-3-oxime':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 'lithium'/exp OR 'valproic acid'/exp OR 'tideglusib'/exp OR 'haloperidol'/exp OR 'olanzapine'/exp) AND ('neoplasm'/exp OR 'neoplasm' OR adenoma*:ti,ab,kw OR anticarcinogen*:ti,ab,kw OR blastoma*:ti,ab,kw OR cancer*:ti,ab,kw OR carcinogen*:ti,ab,kw OR carcinom*: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 leukemi*:ti,ab,kw OR lymphangioma*:ti,ab,kw OR lymphangiomyoma*:ti,ab,kw OR lymphangiosarcoma*:ti,ab,kw OR lymphom*:ti,ab,kw OR malignan*:ti,ab,kw OR melanom*:ti,ab,kw OR meningioma*:ti,ab,kw OR mesenchymoma*:ti,ab,kw OR mesonephroma*:ti,ab,kw OR metasta*:ti,ab,kw OR neoplas*:ti,ab,kw OR neuroma*:ti,ab,kw OR nsclc:ti,ab,kw OR oncogen*:ti,ab,kw OR oncolog*:ti,ab,kw OR paraneoplastic:ti,ab,kw OR plasmacytoma*:ti,ab,kw OR precancerous:ti,ab,kw OR sarcoma*:ti,ab,kw OR teratocarcinoma*:ti,ab,kw OR teratoma*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw)
Cochrane	(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*)

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item 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 to 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 many reviewers 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 report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details 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 each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Yes
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding 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, how many 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 study intervention characteristics 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 summary 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 biases).	Yes
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Yes

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Yes
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	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) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Yes
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Yes
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate 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 assessed.	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
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Yes
	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 review.	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

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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BMJ Open

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

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#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.

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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

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Introduction

The Wnt/β-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/β-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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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 1st, 2024. PubMed, Embase and Cochrane databases were searched. All articles until November 1st 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.

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Critical appraisal

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**).

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.

Study registration: PROSPERO, CRD42021286193

Patient and public involvement

None

Results

Article selection

Our PubMed database search until November 2023 yielded 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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clinical data (35–38). 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 a low risk of bias (**Tables 11&12**). One study by Stritzelberger et al. (**Table 12**) did not show all data concerning VPA (39).

Concerning Lithium, 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 three case-control studies by Hallas et al., Kahan et al. and Tamim et al. (**Table 14**) were subject to a high risk of bias (40–43).

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 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).

Outcomes

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).

Lithium

Nine cohort studies assessed the association between lithium use and cancer 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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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)).

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)).

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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 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. 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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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. 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

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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.

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 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 1st, 2024. Moreover, bias was minimized by using two independent authors in the screening process.

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,

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which results in limitations in drawing an overall conclusion regarding the cancer risk of 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

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.

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.

Statements

Ethics approval

No ethics approval was required for this study

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Table 1. Mechanisms of action of all drugs included

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)
Valproic acid	GSK3beta inhibition(88)

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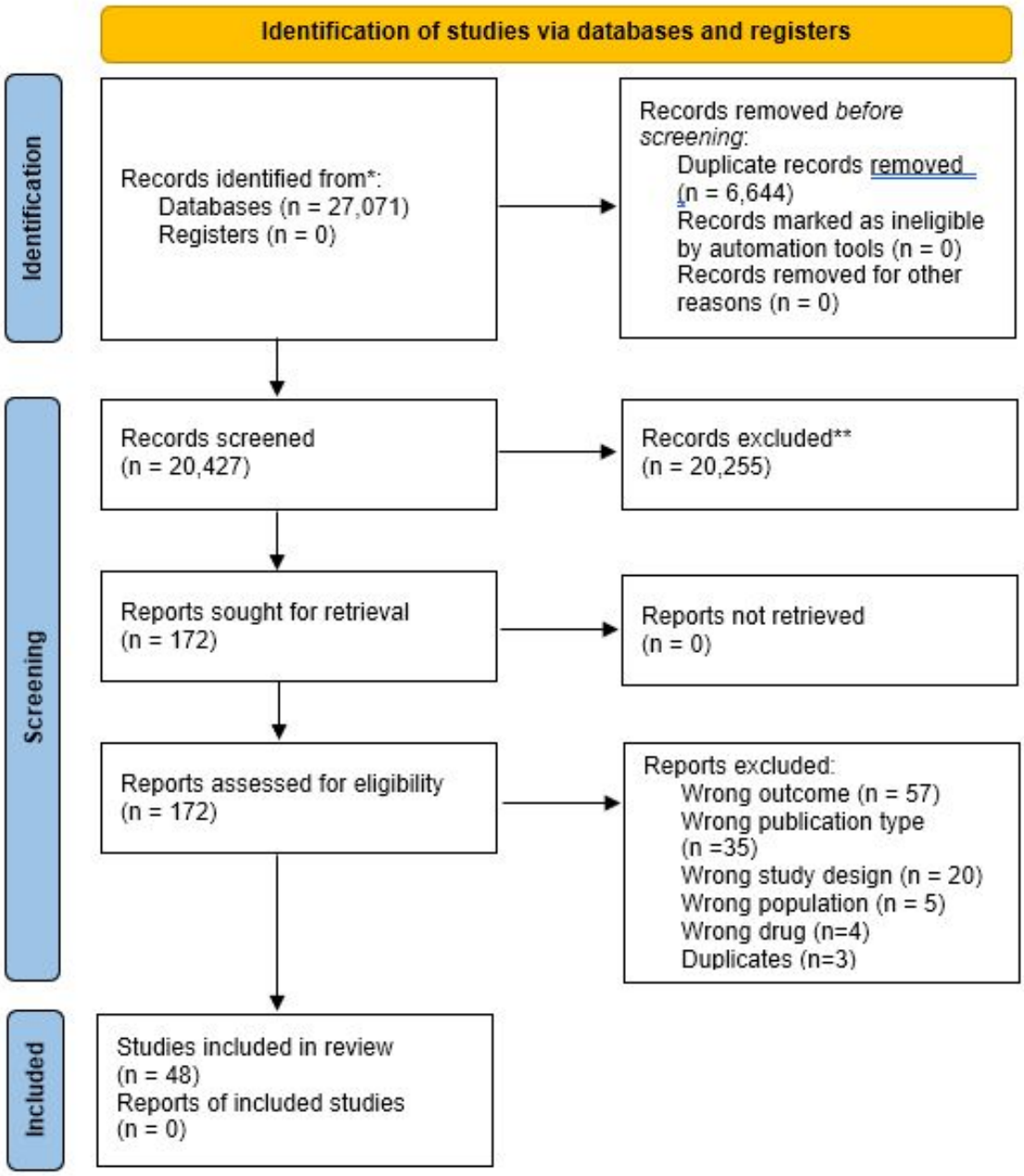

Figure 1: Article selection flow diagram. The identification of studies via databases and registers is presented above. The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion. The protocol was perfomed based on the PRISMA 2020 flow diagram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

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Appendix: Compounds in search string.

AR-A014418

AZD-1080

Chir-99021

CHIR98014

Cimetidine

FX-322

Gemifloxacin

Hydroxychloroquine

Lithium

LY2090314

Olanzapine

SB216763

TDZD8

Tideglusib

TWS119

TWS119

Valproic acid

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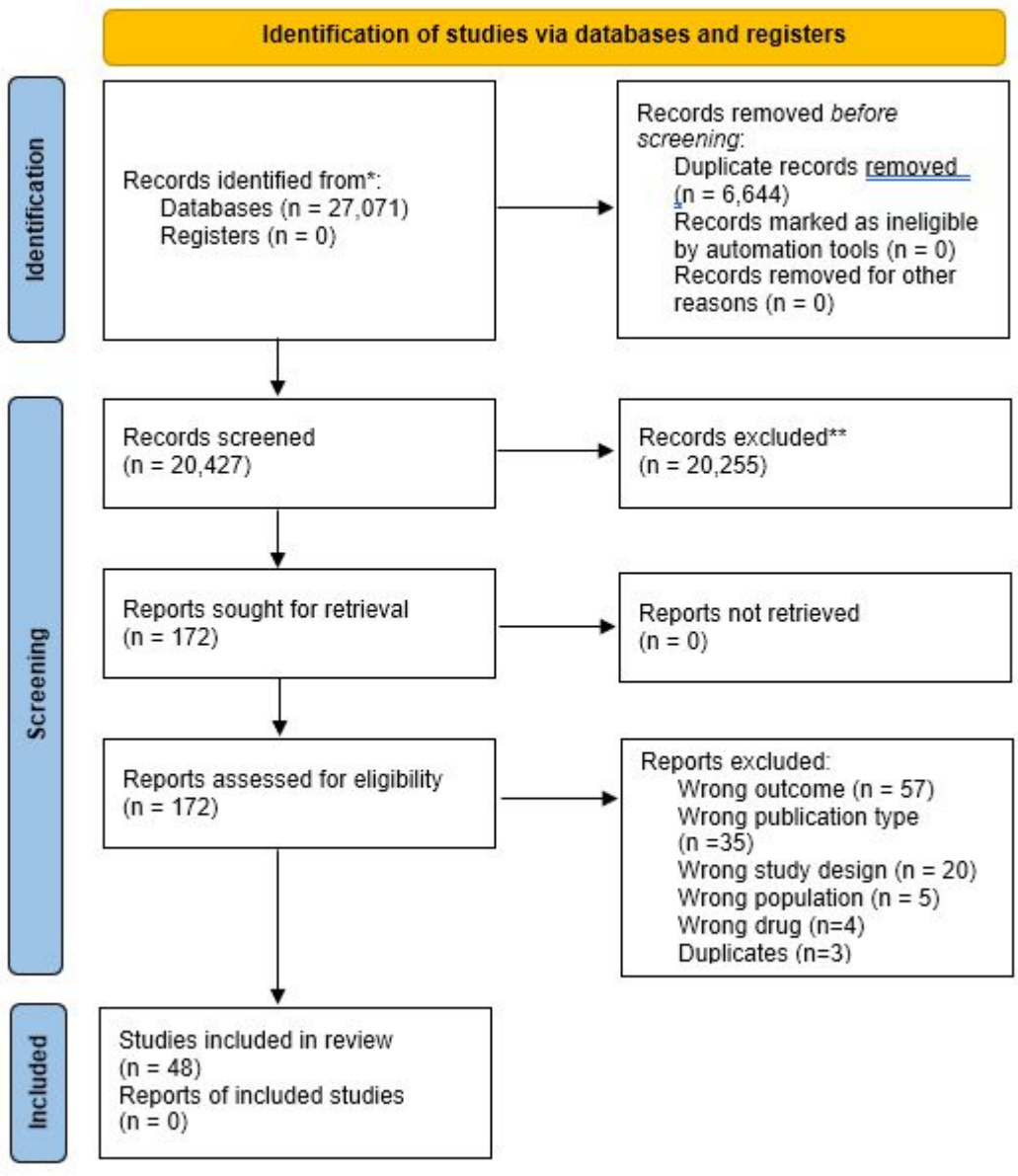

Figure 1: Article selection flow diagram. The identification of studies via databases and registers is presented above. The selection was divided in three stages. Identification in databases and registers. Then screening and lastly inclusion. The protocol was perfomed based on the PRISMA 2020 flow diagram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

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

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Chavez	2020	Retrospective cohort		*	*	*	**	*	*		Good
Lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kaae	2010	population-based cohort study	*	*	*	*	**	*	*	*	Good
Kang	2014	retrospective cohort study		*	*	*	**	*	*	*	Good
Singh	2011	cohort study	*	*	*	*	**	*	*	*	Good
Yang	2022	Nationwide cohort	*	*	*		**	*	*	*	Good

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Table 12. Critical appraisal table for case control studies on the use of VPA

Author	Year	Type of study	Selection (max 1 star)			Comparability (max 2 stars)		Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases and controls	Ascertainment of outcome	Non-response rate	
George	2023	case-control	*	*	*	*	**	*	*	Good
Hallas	2009	case control	*	*	*	*	**	*	*	Good
Li	2024	Nested Case control	*	*	*	*	**	*	*	Good
Kristensen	2019	nested case control	*	*	*	*	*	*	*	Good
Salminen	2016	case-control	*	*	*	*	**	*	*	Good
Stritzelberger	2020	Nested case control	N/A	High risk of bias, not the aim of the study and not all data shown						Poor
Tilhonen	2022	case-control	*	*	*	*	**	*	*	Good

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Table 13. Critical appraisal table for cohort studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star)				Comparibility of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Asgari	2017	retrospective cohort		*	*	*	**	*	*	*	Good
Lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Cohen	1998		*	*	*	*	**	*	*	*	Good
George	2019	restrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	**	*	*		Good
Kessing	2024	Cohort (Population based)	*	*	*	*	**	*	*	*	Good
Martinsson	2016	Cohort nationwide		*	*	*	**	*	*	*	Good
Zaidan	2014	retrospective cohort study	N/A - Data from cohort compared to general population, expressed as standardized incidence ratio; small cohort								Poor

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Table 14. Critical appraisal table for case-control studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star) Comparability				Comparability (Max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Hallas	2009	case control	*	*		*		*	*	Poor
Kahan	2018	Case-control study from large database	Data from large database, scale non-applicable, high risk of bias							Poor
Li	2024	Nested Case control	*	*	*	*	**	*	*	Good
Pottengard	2016 (1)	Nationwide case control study	*	*	*	*	**	*	*	Poor
Pottengard	2016 (2)	Case control study nationwide	*	*	*	*	**	*	*	Good
Tamim	2008	Nested case-control	*	*	*	*	Lithium not main question of study	*	*	Poor

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Table 15. Critical appraisal table for cohort studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Moller	1989	Cohort	No control, high risk of bias								Poor
Rossing	2000	Retrospective cohort study	*	*		*	**	*	*	*	Good
Velicer	2006	Cohort study		*		*	**	*	*	*	Fair

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Table 16. Critical appraisal table for surveillance and case-control studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparibility (Max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Colin Jones	1985	case control study	No representative outcome; already had gastrcic ulcers, only age and sex matched controls							Poor
Colin Jones	1991	surveillance study	No control, N/A							N/A
Coogan	2005	Database study/case-control	*		*		**			Poor
Holly	1997	population-based case-control study				*	**	*		Poor
Mathes	2008	Population based case-control study	*	*	*	*	**	*		Good
Moller	1992	Case-control study	High risk of bias							Poor
Schumacher	1990	Case-control study	*	*			**			Poor

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Table 17. Critical appraisal table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Tilhonen	2022	cohort study	*	*	*	**	*	*	*		Good
Wang	2002	Retrospective cohort	*		*	*	*	*	*	*	Good

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

Author	Year	Type of study	Selection (max 1 star)				Comparibility (max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparibility of cases and controls	Ascertainment of outcome	Non-response rate	
Brainerd	2024	Case Control study	*	*	*	*	**	*	*	Good
Chen	2022	Case-control study	*	*	*	*	**	*	*	Good
Friedman	2020	Case-control	*	*	*	*	**	*	*	Good
Hsieh	2005	Database study/case-control	Scale not fully applicable due to study design, high risk of bia							Poor; N/A
Pottengard	1997	population-based case-control study	*	*	*	*	**	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	*	*	Good

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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	Analysis (95%)	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	HR 0.64 (0.51-0.79)	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%)	1(0.7-1.3)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	0.8 (0.563-1.277)	No	Good
Kaae	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any use: BCC 1.3(1.1-1.4), CMM 1(0.8-1.3), MCC 1.2(0.2-8.7), SCC 1.3(1.1-1.6) Per 5 years of use: BCC 1.1 (0.9-1.4); CMM 1 0.9 (0.5-1.5) MCC *No 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%)	lung (0.96), Head and neck (0.68), prostate (0.97), colon and rectum (0.9), 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 ratio = 1.18 (0.96–1.46)	No	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.817 (0.642-1.032)	No	Good

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Table 3. Data extraction and results table for non-cohort studies on the use of VPA

Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	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	OR (95% CI) 0.85 (0.70-1.04)	no	Good
Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	OR = 1.21 (0.95-1.56)	No	Good
Li	2024	Taiwan	Psychiatric	Matched controls	15540 matched controls	33 cases exposed (8.1%) 1438 cases unexposed (9.1%)	OR=0.53 (0.39-0.56)	Decrease	Good
Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	1623 (0.2%)	162 (0.2%)	No significant difference, OR not reported	No	Good
Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	X	X	0.62 (0.42-0.92) 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	p=0.7-0	No	Poor

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Table 4. Data extraction and results table for cohort studies on the use of lithium

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias 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)	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%)	1(0.6-1.6)	No	Good
Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	19/609 (3.12%)	1.19 (0.71-2.01)	No	Good.
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)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	6 patients (1.6%)	0.426 (0.186-0.975)	No, decrease	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)	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% (-9.7%; 4.1%) Cohort 2: -3.0% (-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%)	1.04 (0.89-1.23)	No	Good
Zaidan	2014	France	Bipolar disorder	Matched (EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	p=0.04	Yes	Poor

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

Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Hallas	2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	1.19 (1.03-1.37)	Yes, minimal (not all data shown, not the main question)	Poor
Kahan	2018	Israel	Bipolar disorder	All members if LHS (Health insurance company)	Expected cancer cases: 68	Expected cases Lithium group: 61.09	standardized incidence ratio male 0.93(0.6-1.38); female 1.25 (0.91-1.6)	No	Poor
Li	2024	Taiwan	Psychiatric	Matched controls	15,540 matched controls	45 cases exposed (9.1%) 1470 cases unexposed (9.1%)	OR = 0.81 (0.5 1.12); p=0.20	No	Good
Pottengard	2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	1.01(0.86-1.1	No	Good
Pottengard	2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	OR = 1.3 (0.7-2.1)	No	Good
Tamim	2008	Canada	Psychiatric	No history of cancer	257 (0.8%)	69 (0.9%);	No significant difference OR not reported	No	Poor

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Table 6. Data extraction and results table for cohort studies on the use of cimetidine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Exposure duration	Risk of bias verdict
Moller	1989	Denmark	Gastro-intestinal	No control, national incidence			RR= 1.5 (p<0.001)	Yes	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)	No	not specified	Good, however not all data shown.
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)	No	not specified	Fair

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Table 7. Data extraction and results table for surveillance and case-control studies for the use of cimetidine

Type of study	Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Surveillance	Colin jones	1991	UK	Gastro-intestinal	x	x	111/9928 (1.1%)	NO control group!	No	Poor
	Colin jones	1985	UK	Gastro-intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	not done	No	N/A
Case-control	Coogan	2005	USA	Gastro-intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	OR=0.9 (0.6-1.2)	No	Poor
	Holly	1997	USA	Gastro-intestinal	Never use	X	X	OR 0.39 (0.17-0.89)	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: Ductal carcinoma:OR= 1.1 (0.8-1.5); Lobular carcinoma OR = 1.0 (0.7-1.6); >2 years use ductal carcinoma, 0.9 (0.5-1.5) lobular carcinoma, 1.1(0.6-1.9)	No	Good
	Moller	1992	Denmark	Gastro-intestinal	Matched controls Group health national pharmacy			OR = 2.1 (0.7-6.3)	No	Poor
	Schumacher	1990	USA	gastro-intestinal	Non users	x	x	OR = 2.1 (95% CI = 0.7-6.3)	No	Poor

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Table 8. Data extraction and results table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	HR = 1.05 (0.9 1.21	No	Good
Tiihonen	2022	Finland	Clozapine (schizophrenia)	matched controls (schizophrenia patient without cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted OR 3.5 (2.22-5.05 >5000 defined daily dose cumulative exposure	Yes, hematologic	Good

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Table 9. Data extraction and results table for case-control studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Drug of interest	Control condition	Controls	Cases	Analysis (95% CI)	Increase in cancer prevalence	Risk of bias verdict
Brainerd	2024	USA	Clozapine	Matched controls	23,043 (4.1%)	2,306(5.3%)	OR = 1.31 (1.08-1.60)	Yes	Good
Chen	2022	Taiwan	Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% CI is 1.75 (1.31–2.33)	yes	Good
			Olanzapine	Matched controls	63/37908	13/9502	OR (95% CI 0.72 (0.38–1.37)	no	
			Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% CI 0.14 (0.56–3.38)	no	
Friedman	2020	USA	Haloperidol	Not treated with haloperidol	39553/1962602 (2.0%)	4/352 (1.1%)	OR = 0.54 (0.2-1.44)	No	Good
					576	4/576 (0.7%)	OR = 0.32 (0.1-1.84)	No, decrease	
					2008	30/2008 (1.5%)	OR = 0.69 (0.4-0.99)	No, decrease	
Hsieh	2019	Taiwan	Clozapine	Non-gastric cancer	92 (0.06%)	4 (0.01%)	OR = 0.35 (0.1-0.97)	No, decrease	N/A
			Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (0.14-0.46)	No, decrease	
			Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (0.05-0.35)	No, decrease	
Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted OR 1: 1.30 (1.09-1.56) Adjusted OR 2: 1.15 (0.9-1.47)	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 (2.07-4.17)	Yes, hematologic cancers	Good

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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	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Lertxundi	2019	Clozapine	x	Pituary tumor	17 cases	PRR 0.98 (0.5-1.8)	No	N/A
		Haloperidol	x	Pituary tumor	11 cases	PRR 7.0(4.35-11.3)	Possibly	
		Olanzapine	x	Pituary tumor	17 cases	PRR 2.53 (1.57-4.1)	Possibly	
Szarfman	2006	Clozapine	x	Pituary tumor	4 cases	ROR 0.9 (0.4-1.7)	No	N/A
		Haloperidol	x	Pituary tumor	9 cases	ROR 5.6 (2.9-13)	Possibly	
		Olanzapine	x	Pituary tumor	11 cases	ROR 2.3 (1.4-3.7)	Possibly	
Chretien	2021	Clozapine	x	Hematologic malignancies	275	aROR 9.14 (7.75-10.77)	Possibly	N/A
		Olanzapine	x	Hematologic malignancies	68	aROR 0.88 (0.66- 1.16)	No	
Maeshima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1.00 (0.07, 3.51) ROR	No	N/A
		Olanzapine	x	Benign and malignant breast cancer	1825	2.00 (0.07, 3.51) ROR	No	
Dawson	2023	Clozapine	x	Hematological	104/384	excess of hematological cancers in people exposed to clozapine	Possibly	N/A
				Neoplasm	61/384		No	
				Lung	50*384		No	
				Breast	37/384		No	
				Colorectal	28/384		No	
				Brain	18/384		No	
				Skin	17/384		No	
				Esophagogastric	11/384		No	
				Pancreatic	10/384		No	
				Urological	9/384		No	
				Testicular	8/384		No	
				Hepatic	7/384		No	
				ENT	6/384		No	
				Gynecological	<5/384		No	
				others	14/384		No	
Uwai	2024	Clozapine	x	All non-hematologic malignancies	1668	Reporting Odds Ratio= 1.28 (1.22-1.34)	Possibly	N/A

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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	Analysis (95%)	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	HR 0.64 (0.51-0.79)	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%)	1(0.7-1.3)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	0.8 (0.563-1.277)	No	Good
Kaae	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any use: BCC 1.3(1.1-1.4), CMM 1(0.8-1.3), MCC 1.2(0.2-8.7), SCC 1.3(1.1-1.6) Per 5 years of use: BCC 1.1 (0.9-1.4); CMM 1 0.9 (0.5-1.5) MCC *No 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%)	lung (0.96), Head and neck (0.68), prostate (0.97), colon and rectum (0.9), 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 ratio = 1.18 (0.96–1.46)	No	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.817 (0.642-1.032)	No	Good

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Table 3. Data extraction and results table for non-cohort studies on the use of VPA

Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	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	OR (95% CI) 0.85 (0.70-1.04)	no	Good
Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	OR = 1.21 (0.95-1.56)	No	Good
Li	2024	Taiwan	Psychiatric	Matched controls	15540 matched controls	33 cases exposed (8.1%) 1438 cases unexposed (9.1%)	OR=0.53 (0.39-0.56)	Decrease	Good
Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	1623 (0.2%)	162 (0.2%)	No significant difference, OR not reported	No	Good
Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	X	X	0.62 (0.42-0.92) 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	p=0.7-0	No	Poor

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Table 4. Data extraction and results table for cohort studies on the use of lithium

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias 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)	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%)	1(0.6-1.6)	No	Good
Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	19/609 (3.12%)	1.19 (0.71-2.01)	No	Good.
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)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	6 patients (1.6%)	0.426 (0.186-0.975)	No, decrease	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)	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% (-9.7%; 4.1%) Cohort 2: -3.0% (-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%)	1.04 (0.89-1.23)	No	Good
Zaidan	2014	France	Bipolar disorder	Matched (EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	p=0.04	Yes	Poor

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

Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Hallas	2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	1.19 (1.03-1.37)	Yes, minimal (not all data shown, not the main question)	Poor
Kahan	2018	Israel	Bipolar disorder	All members if LHS (Health insurance company)	Expected cancer cases: 68	Expected cases Lithium group: 61.09	standardized incidence ratio male 0.93(0.6-1.38); female 1.25 (0.91-1.6)	No	Poor
Li	2024	Taiwan	Psychiatric	Matched controls	15,540 matched controls	45 cases exposed (9.1%) 1470 cases unexposed (9.1%)	OR = 0.81 (0.5 1.12); p=0.20	No	Good
Pottengard	2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	1.01(0.86-1.1	No	Good
Pottengard	2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	OR = 1.3 (0.7-2.1)	No	Good
Tamim	2008	Canada	Psychiatric	No history of cancer	257 (0.8%)	69 (0.9%);	No significant difference OR not reported	No	Poor

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Table 6. Data extraction and results table for cohort studies on the use of cimetidine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Exposure duration	Risk of bias verdict
Moller	1989	Denmark	Gastro-intestinal	No control, national incidence			RR= 1.5 (p<0.001)	Yes	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)	No	not specified	Good, however not all data shown.
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)	No	not specified	Fair

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Table 7. Data extraction and results table for surveillance and case-control studies for the use of cimetidine

Type of study	Study	Year	Location	Indication for use	Control condition	Controls	Cases	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Surveillance	Colin jones	1991	UK	Gastro-intestinal	x	x	111/9928 (1.1%)	NO control group!	No	Poor
	Colin jones	1985	UK	Gastro-intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	not done	No	N/A
Case-control	Coogan	2005	USA	Gastro-intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	OR=0.9 (0.6-1.2)	No	Poor
	Holly	1997	USA	Gastro-intestinal	Never use	X	X	OR=0.39 (0.17-0.89)	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: Ductal carcinoma:OR= 1.1 (0.8-1.5); Lobular carcinoma OR = 1.0 (0.7-1.6); >2 years use ductal carcinoma, 0.9 (0.5-1.5) lobular carcinoma, 1.1(0.6-1.9)	No	Good
	Moller	1992	Denmark	Gastro-intestinal	Matched controls Group health national pharmacy			OR = 2.1 (0.7-6.3)	No	Poor
	Schumacher	1990	USA	gastro-intestinal	Non users	x	x	OR = 2.1 (95% CI = 0.7-6.3)	No	Poor

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Table 8. Data extraction and results table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	HR = 1.05 (0.9 1.21)	No	Good
Tiihonen	2022	Finland	Clozapine (schizophrenia)	matched controls (schizophrenia patient without cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted OR 3.25 (2.22-5.05) >5000 defined daily dose cumulative exposure	Yes, hematologic	Good

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Table 9. Data extraction and results table for case-control studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Drug of interest	Control condition	Controls	Cases	Analysis (95% CI)	Increase in cancer prevalence	Risk of bias verdict
Brainerd	2024	USA	Clozapine	Matched controls	23,043 (4.1%)	2,306(5.3%)	OR = 1.31 (1.08-1.60)	Yes	Good
Chen	2022	Taiwan	Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% CI is 3.75 (1.31–10.7	yes	Good
			Olanzapine	Matched controls	63/37908	13/9502	OR (95% CI 1.72 (0.38–7.72	no	
			Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% CI 1.4 (0.56–3.5	no	
Friedman	2020	USA	Haloperidol	Not treated with haloperidol	39553/1962602 (2.0%)	4/352 (1.1%)	OR = 0.54 (0.2-1.44)	No	Good
					576	4/576 (0.7%)	OR = 0.32 (0.1-1.84)	No, decrease	
					2008	30/2008 (1.5%)	OR = 0.69 (0.4-0.99)	No, decrease	
Hsieh	2019	Taiwan	Clozapine	Non-gastric cancer	92 (0.06%)	4 (0.01%)	OR = 0.35 (0.1-0.97)	No, decrease	N/A
			Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (0.14-0.46)	No, decrease	
			Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (0.05-0.35)	No, decrease	
Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted OR 1: 1.30 (1.09-1.56) Adjusted OR 2: 1.15 (0.9-1.47)	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 (2.07-4.17)	Yes, hematologic cancers	Good

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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	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Lertxundi	2019	Clozapine	x	Pituary tumor	17 cases	PRR 0.98 (0.5-1.8)	No	N/A
		Haloperidol	x	Pituary tumor	11 cases	PRR 7.0(4.35-11.3)	Possibly	
		Olanzapine	x	Pituary tumor	17 cases	PRR 2.53 (1.57-4.1)	Possibly	
Szarfman	2006	Clozapine	x	Pituary tumor	4 cases	ROR 0.9 (0.4-1.7)	No	N/A
		Haloperidol	x	Pituary tumor	9 cases	ROR 5.6 (2.9-13)	Possibly	
		Olanzapine	x	Pituary tumor	11 cases	ROR 2.3 (1.4-3.7)	Possibly	
Chretien	2021	Clozapine	x	Hematologic malignancies	275	aROR 9.14 (7.75-10.77)	Possibly	N/A
		Olanzapine	x	Hematologic malignancies	68	aROR 0.88 (0.66- 1.16)	No	
Maeshima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1.00 (0.07, 3.51) ROR	No	N/A
		Olanzapine	x	Benign and malignant breast cancer	1825	2.00 (0.07, 3.51) ROR	No	
Dawson	2023	Clozapine	x	Hematological	104/384	excess of hematological cancers in people exposed to clozapine	Possibly	N/A
				Neoplasm	61/384		No	
				Lung	50*384		No	
				Breast	37/384		No	
				Colorectal	28/384		No	
				Brain	18/384		No	
				Skin	17/384		No	
				Esophagogastric	11/384		No	
				Pancreatic	10/384		No	
				Urological	9/384		No	
				Testicular	8/384		No	
				Hepatic	7/384		No	
				ENT	6/384		No	
				Gynecological	<5/384		No	
				others	14/384		No	
Uwai	2024	Clozapine	x	All non-hematologic malignancies	1668	Reporting Odds Ratio= 1.28 (1.22-1.34)	Possibly	N/A

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

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Chavez	2020	Retrospective cohort		*	*	*	**	*	*		Good
Lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kaae	2010	population-based cohort study	*	*	*	*	**	*	*	*	Good
Kang	2014	retrospective cohort study		*	*	*	**	*	*	*	Good
Singh	2011	cohort study	*	*	*	*	**	*	*	*	Good
Yang	2022	Nationwide cohort	*	*	*		**	*	*	*	Good

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Table 12. Critical appraisal table for case control studies on the use of VPA

Author	Year	Type of study	Selection (max 1 star)			Comparability (max 2 stars)		Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases and controls	Ascertainment of outcome	Non-response rate	
George	2023	case-control	*	*	*	*	**	*	*	Good
Hallas	2009	case control	*	*	*	*	**	*	*	Good
Li	2024	Nested Case control	*	*	*	*	**	*	*	Good
Kristensen	2019	nested case control	*	*	*	*	*	*	*	Good
Salminen	2016	case-control	*	*	*	*	**	*	*	Good
Stritzelberger	2020	Nested case control	N/A	High risk of bias, not the aim of the study and not all data shown						Poor
Tilhonen	2022	case-control	*	*	*	*	**	*	*	Good

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Table 13. Critical appraisal table for cohort studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star)				Comparibility of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Asgari	2017	retrospective cohort		*	*	*	**	*	*	*	Good
Lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Cohen	1998		*	*	*	*	**	*	*	*	Good
George	2019	restrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	**	*	*		Good
Kessing	2024	Cohort (Population based)	*	*	*	*	**	*	*	*	Good
Martinsson	2016	Cohort nationwide		*	*	*	**	*	*	*	Good
Zaidan	2014	retrospective cohort study	N/A - Data from cohort compared to general population, expressed as standardized incidence ratio; small cohort								Poor

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Table 14. Critical appraisal table for case-control studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star) Comparability				Comparability (Max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Hallas	2009	case control	*	*		*		*	*	Poor
Kahan	2018	Case-control study from large database	Data from large database, scale non-applicable, high risk of bias							Poor
Li	2024	Nested Case control	*	*	*	*	**	*	*	Good
Pottengard	2016 (1)	Nationwide case control study	*	*	*	*	**	*	*	Poor
Pottengard	2016 (2)	Case control study nationwide	*	*	*	*	**	*	*	Good
Tamim	2008	Nested case-control	*	*	*	*	Lithium not main question of study	*	*	Poor

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Table 15. Critical appraisal table for cohort studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Moller	1989	Cohort	No control, high risk of bias								Poor
Rossing	2000	Retrospective cohort study	*	*		*	**	*	*	*	Good
Velicer	2006	Cohort study		*		*	**	*	*	*	Fair

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Table 16. Critical appraisal table for surveillance and case-control studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparibility (Max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Colin Jones	1985	case control study	No representative outcome; already had gastrcic ulcers, only age and sex matched cont							Poor
Colin Jones	1991	surveillance study	No control, N/A							N/A
Coogan	2005	Database study/case-control	*		*		**			Poor
Holly	1997	population-based case-control study				*	**	*		Poor
Mathes	2008	Population based case-control study	*	*	*	*	**	*		Good
Moller	1992	Case-control study	High risk of bias							Poor
Schumacher	1990	Case-control study	*	*			**			Poor

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Table 17. Critical appraisal table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Tilhonen	2022	cohort study	*	*	*	**	*	*	*		Good
Wang	2002	Retrospective cohort	*		*	*	*	*	*	*	Good

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

Author	Year	Type of study	Selection (max 1 star)				Comparibility (max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparibility of cases and controls	Ascertainment of outcome	Non-response rate	
Brainerd	2024	Case Control study	*	*	*	*	**	*	*	Good
Chen	2022	Case-control study	*	*	*	*	**	*	*	Good
Friedman	2020	Case-control	*	*	*	*	**	*	*	Good
Hsieh	2005	Database study/case-control	Scale not fully applicable due to study design, high risk of bia							Poor; N/A
Pottengard	1997	population-based case-control study	*	*	*	*	**	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	*	*	Good

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

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

Strengths and limitations of this study

- Inclusion of all study designs, providing a broad overview of studies covering the topic.
- Substantial heterogeneity in study designs, inclusion of types of patients, and conditions.
- We cannot generalize the outcomes based on the broad mechanism of action of the compounds included.

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

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INTRODUCTION

The Wnt/β-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/β-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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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 1st, 2024. PubMed, Embase and Cochrane databases were searched. All articles until November 1st 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**.

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 S2-S10**). No authors were contacted due to data unavailability after inclusion.

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Critical appraisal

The methodological quality of included articles was assessed by two reviewers (AA. N.S-C) 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: selection bias, comparability of cohorts, and outcome (**Tables S11-S18**).

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.

Study registration

PROSPERO, CRD42021286193.

Patient and public involvement

None.

RESULTS

Article selection

Our PubMed database search until November 2023 yielded 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 S2-S10**, 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

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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 clinical data [35–38]. 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 a low risk of bias (**Tables S11&S12**). One study by Stritzelberger et al. (**Table S12**) did not show all data concerning VPA [39].

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

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

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

Outcomes

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

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([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)).

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)).

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].

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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).

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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However, the database studies performed by Lertxundi et al. and Szarfman et al. suggested an increased risk of pituitary tumors of subjects exposed to olanzapine [78] (PRR= 2.53, (1.57-4.1)); [79] 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 [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)).

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**)

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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 Tiihonen 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

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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 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.

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 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 1st, 2024. Moreover, bias was minimized by using two independent authors in the screening process.

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, which results in limitations in drawing an overall conclusion regarding the cancer risk of 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

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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

The authors have no competing interest to declare.

Data availability statement

No additional data available.

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Table 1. Mechanisms of action of all drugs included

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)
Valproic acid	GSK3beta inhibition(88)

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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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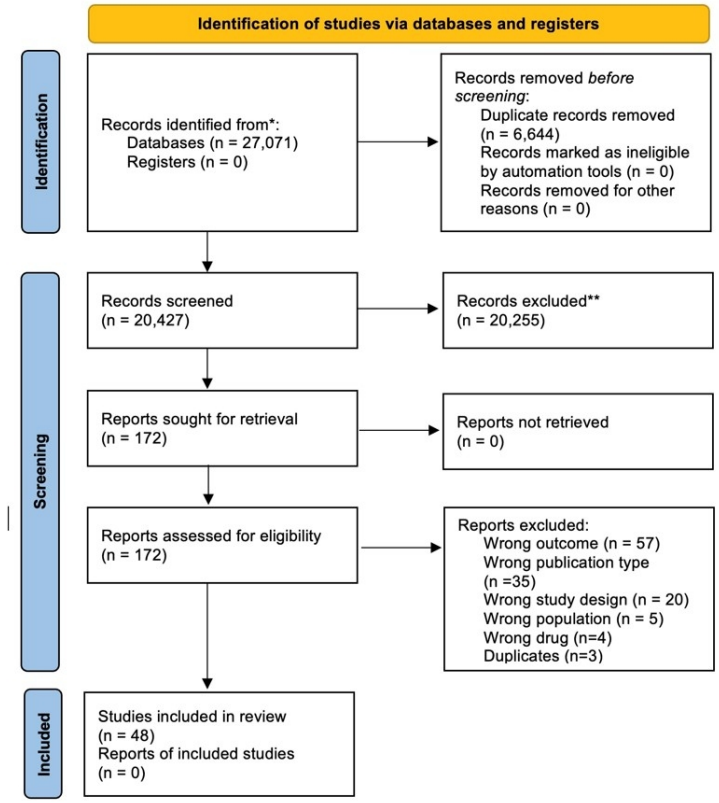

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Table S1: The search strategy

Database	Search string
PubMed	(Lithium[Title/Abstract] OR valpr*[Title/Abstract] OR tideglusib[Title/Abstract] OR AZD1080[Title/Abstract] 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 Clozapine [Title/Abstract] OR Haloperidol [Title/Abstract] OR Kenpaullone [Title/Abstract] OR L803mts [Title/Abstract] OR lithium[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 carcinosarcoma*[tw] OR chordoma*[tw] OR germinoma*[tw] OR gonadoblastoma*[tw] OR hepatoblastoma*[tw] OR hodgkin disease[tw] OR hodgkin's disease[tw] OR hodgkins disease[tw] OR leukemi*[tw] OR lymphangioma*[tw] OR lymphangiomyoma*[tw] OR lymphangiosarcoma*[tw] OR lymphom*[tw] OR malignan*[tw] OR melanom*[tw] OR meningioma*[tw] OR mesenchymoma*[tw] OR mesonephroma*[tw] OR metasta*[tw] OR neoplas*[tw] OR neuroma*[tw] OR nsclc[tw] OR oncogen*[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 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 'cimetidine':ti,ab,kw OR 'olanzapine':ti,ab,kw OR '6-bromoindirubin-3-oxime':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 'lithium'/exp OR 'valproic acid'/exp OR 'tideglusib'/exp OR 'haloperidol'/exp OR 'olanzapine'/exp) AND ('neoplasm'/exp OR 'neoplasm' OR adenoma*:ti,ab,kw OR anticarcinogen*:ti,ab,kw OR blastoma*:ti,ab,kw OR cancer*:ti,ab,kw OR carcinogen*:ti,ab,kw OR carcinom*: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 leukemi*:ti,ab,kw OR lymphangioma*:ti,ab,kw OR lymphangiomyoma*:ti,ab,kw OR lymphangiosarcoma*:ti,ab,kw OR lymphom*:ti,ab,kw OR malignan*:ti,ab,kw OR melanom*:ti,ab,kw OR meningioma*:ti,ab,kw OR mesenchymoma*:ti,ab,kw OR mesonephroma*:ti,ab,kw OR metasta*:ti,ab,kw OR neoplas*:ti,ab,kw OR neuroma*:ti,ab,kw OR nsclc:ti,ab,kw OR oncogen*:ti,ab,kw OR oncolog*:ti,ab,kw OR paraneoplastic:ti,ab,kw OR plasmacytoma*:ti,ab,kw OR precancerous:ti,ab,kw OR sarcoma*:ti,ab,kw OR teratocarcinoma*:ti,ab,kw OR teratoma*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw)
Cochrane	(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*)

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Table S2. 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	Analysis (95%)	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	HR 0.64 (0.51-0.79)	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%)	1(0.7-1.3)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	3.4%	2.0%	0.8 (0.563-1.277)	No	Good
Kaae	2010	Denmark	Any use	Non users of photosensitising medication	Not shown	Not shown	Any use: BCC 1.3(1.1-1.4), CMM 1(0.8-1.3), MCC 1.2(0.2-8.7), SCC 1.3(1.1-1.6) Per 5 years of use: BCC 1.1 (0.9-1.4); CMM 1 0.9 (0.5-1.5) MCC *No 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%)	lung (0.96), Head and neck (0.68), prostate (0.97), colon and rectum (0.9), 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 ratio = 1.18 (0.96–1.46)	No	Good
Yang	2022	Taiwan	Neurologic	Matched controls	2197(4.97%)	492 (4.45%)	0.817 (0.642-1.032)	No	Good

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Table S3. Data extraction and results table for non-cohort studies on the use of VPA

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	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	OR (95% CI) 0.85 (0.70-1.04)	no	Good
Hallas	2009	Denmark	Neurologic	Randomly selected among all Danish citizens	260 exposed 595256 unexposed	81 exposed/148617 unexposed	OR = 1.21 (0.95-1.56)	No	Good
Li	2024	Taiwan	Psychiatric	Matched controls	15540 matched controls	33 cases exposed (8.1%) 1438 cases unexposed (9.1%)	OR=0.58 (0.39-0.56)	Decrease	Good
Kristensen	2019	Denmark	Any use	Patients treated with antiepileptic drugs and no VPA	1623 (0.2%)	162 (0.2%)	No significant difference, OR not reported	No	Good
Salminen	2016	Finland	Neurologic (epilepsy)	Matched controls	X	X	0.62 (0.42-0.92) 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	p=0.7-0	No	Poor

Table S4. Data extraction and results table for cohort studies on the use of lithium

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Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias 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)	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%)	1(0.6-1.6)	No	Good
Cohen	1998	Israel	Psychiatric	Other patients treated in index hospital (3 mental health centers)	63/ 2396 (2.63%)	19/609 (3.12%)	1.19 (0.71-2.01)	No	Good.
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)	No	Good
Huang	2016	Taiwan	Bipolar disorder	Treated with anticonvulsants	86 patients (2.6%)	6 patients (1.6%)	0.426 (0.186-0.975)	No, decrease	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)	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% (-9.7%; 4.1%) Cohort 2: -3.0% (-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%)	1.04 (0.89-1.23)	No	Good
Zaidan	2014	France	Bipolar disorder	Matched (EGFR, age) controls	1/340 (0.3%)	7/170 (4.1%)	p=0.04	Yes	Poor

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Table S5. Data extraction and results table for case-control studies on the use of lithium

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Hallas	2009	Denmark	Any use	Matched (age/sex) controls	Controls: 260 exposed, 595256 unexposed	779/595397	1.19 (1.03-1.38)	Yes, minimal (not all data shown, not the main question)	Poor
Kahan	2018	Israel	Bipolar disorder	All members if LHS (Health insurance company)	Expected cancer cases: 68	Expected cases Lithium group: 61.09	standardized incidence ratio men 0.93(0.6-1.38); female 1.25 (0.91-1.62)	No	Poor
Li	2024	Taiwan	Psychiatric	Matched controls	15,540 matched controls	45 cases exposed (9.1%) 1470 cases unexposed (9.1%)	OR = 0.81 (0.59-1.12); p=0.20	No	Good
Pottengard	2016a	Denmark	Any use	Matched (age/sex) controls	Not reported	159/1571	1.01(0.86-1.19)	No	Good
Pottengard	2016b	Denmark	Any use	Matched (age/sex) controls	6453/257978 (2.5%)	14/461 (3.0%)	OR = 1.3 (0.7-2.1)	No	Good
Tamim	2008	Canada	Psychiatric	No history of cancer	257 (0.8%)	69 (0.9%);	No significant difference OR not reported	No	Poor

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Table S6. Data extraction and results table for cohort studies on the use of cimetidine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Exposure duration	Risk of bias verdict
Moller	1989	Denmark	Gastro-intestinal	No control, national incidence			RR= 1.5 (p<0.001)	Yes	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)	No	not specified	Good, however not all data shown.
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)	No	not specified	Fair

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Table S7. Data extraction and results table for surveillance and case-control studies for the use of cimetidine

Type of study	Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Surveillance	Colin jones	1991	UK	Gastro-intestinal	x	x	111/9928 (1.1%)	NO control group!	No	Poor
	Colin jones	1985	UK	Gastro-intestinal	never users	255/9140 (2.8%)	449/9809 (4.6%)	not done	No	N/A
Case-control	Coogan	2005	USA	Gastro-intestinal	Admitted to hospital	102 regular users; 7.926 non-users	68 regular users; 6.591 non-users	OR=0.9 (0.6-1.2)	No	Poor
	Holly	1997	USA	Gastro-intestinal	Never use	X	X	OR 0.39 (0.17-0.89)	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: Ductal carcinoma:OR= 1.1 (0.8-1.5); Lobular carcinoma OR = 1.0 (0.7-1.6); >2 years use ductal carcinoma, 0.9 (0.5-1.5) lobular carcinoma, 1.1(0.6-1.9)	No	Good
	Moller	1992	Denmark	Gastro-intestinal	Matched controls Group health national pharmacy			OR = 2.1 (0.7-6.3)	No	Poor
	Schumacher	1990	USA	gastro-intestinal	Non users	x	x	OR = 2.1 (95% CI = 0.7-6.3)	No	Poor

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Table S8. Data extraction and results table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Indication for use	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Wang	2002	USA	Haloperidol, all exposed individuals	matched controls	1228(0.052%)	240 (0.052%)	HR = 1.05 (0.9 1.21)	No	Good
Tiihonen	2022	Finland	Clozapine (schizophrenia)	matched controls (schizophrenia patient without cancer)	235/ 44171 (0.5%)	102/13712 (0.7%)	Adjusted OR 3.25 (2.22-5.05) >5000 defined daily dose cumulative exposure	Yes, hematologic	Good

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Table S9. Data extraction and results table for case-control studies on the use of haloperidol, clozapine, and olanzapine

Study	Year	Location	Drug of interest	Control condition	Cancer risk Control group	Cancer risk Wnt group = prevalence	Analysis (95% CI)	Increase in cancer prevalence	Risk of bias verdict
Brainerd	2024	USA	Clozapine	Matched controls	23,043 (4.1%)	2,306(5.3%)	OR = 1.31 (1.08-1.60)	Yes	Good
Chen	2022	Taiwan	Haloperidol	Matched controls	184/37908 (cancer free control)	80/9502 (with endometrial cancer)	OR (95% CI is 3.75 (1.31–3	yes	Good
			Olanzapine	Matched controls	63/37908	13/9502	OR (95% CI 1.72 (0.38–3	no	
			Clozapine	Matched controls	35/37908 (cancer free)	11/9502 (endometrial cancer)	OR (95% CI 1.4 (0.56–3	no	
Friedman	2020	USA	Haloperidol	Not treated with haloperidol	39553/1962602 (2.0%)	4/352 (1.1%)	OR = 0.54 (0.2 1.44)	No	Good
					576	4/576 (0.7%)	OR = 0.32 (0.1 0.84)	No, decrease	
					2008	30/2008 (1.5%)	OR = 0.69 (0.4 0.99)	No, decrease	
Hsieh	2019	Taiwan	Clozapine	Non-gastric cancer	92 (0.06%)	4 (0.01%)	OR = 0.35 (0.1 0.97)	No, decrease	N/A
			Haloperidol	Non-gastric cancer	300/ 163430 (0.18%)	11/34470= 0.03%	OR = 0.25 (0.14-0.46)	No, decrease	
			Olanzapine	Non-gastric cancer	212 (0.13%)	4 (0.01%)	OR = 0.13 (0.05 0.35)	No, decrease	
Pottengard	2018	Denmark	Olanzapine	Never used olanzapine	55409	139	Adjusted OR 1: 1.30 (1.09-1.56) Adjusted OR 2: 1.15 (0.9-1.47)	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 (2.07-4.17)	Yes, hematologic cancers	Good

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Table S10. 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	Analysis (95%)	Increase in cancer prevalence	Risk of bias verdict
Lertxundi	2019	Clozapine	x	Pituary tumor	17 cases	PRR 0.98 (0.5-1.8)	No	N/A
		Haloperidol	x	Pituary tumor	11 cases	PRR 7.0(4.35-11.3)	Possibly	
		Olanzapine	x	Pituary tumor	17 cases	PRR 2.53 (1.57-4.1)	Possibly	
Szarfman	2006	Clozapine	x	Pituary tumor	4 cases	ROR 0.9 (0.4-1.7)	No	N/A
		Haloperidol	x	Pituary tumor	9 cases	ROR 5.6 (2.9-13)	Possibly	
		Olanzapine	x	Pituary tumor	11 cases	ROR 2.3 (1.4-3.7)	Possibly	
Chretien	2021	Clozapine	x	Hematologic malignancies	275	aROR 9.14 (7.75-10.77)	Possibly	N/A
		Olanzapine	x	Hematologic malignancies	68	aROR 0.88 (0.66- 1.16)	No	
Maeshima	2021	Haloperidol	x	Benign and malignant breast cancer	939	1.00 (0.07, 3.51) ROR	No	N/A
		Olanzapine	x	Benign and malignant breast cancer	1825	2.00 (0.07, 3.51) ROR	No	
Dawson	2023	Clozapine	x	Hematological	104/384	excess of hematological cancers in people exposed to clozapine	Possibly	N/A
				Neoplasm	61/384		No	
				Lung	50*384		No	
				Breast	37/384		No	
				Colorectal	28/384		No	
				Brain	18/384		No	
				Skin	17/384		No	
				Esophagogastric	11/384		No	
				Pancreatic	10/384		No	
				Urological	9/384		No	
				Testicular	8/384		No	
				Hepatic	7/384		No	
				ENT	6/384		No	
				Gynecological	<5/384		No	
				others	14/384		No	
Uwai	2024	Clozapine	x	All non-hematologic malignancies	1668	Reporting Odds Ratio= 1.28 (1.22-1.34)	Possibly	N/A

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

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Chavez	2020	Retrospective cohort		*	*	*	**	*	*		Good
Lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kaae	2010	population-based cohort study	*	*	*	*	**	*	*	*	Good
Kang	2014	retrospective cohort study		*	*	*	**	*	*	*	Good
Singh	2011	cohort study	*	*	*	*	**	*	*	*	Good
Yang	2022	Nationwide cohort	*	*	*		**	*	*	*	Good

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Table S12. Critical appraisal table for case control studies on the use of VPA

Author	Year	Type of study	Selection (max 1 star)			Comparability (max 2 stars)		Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases and controls	Ascertainment of outcome	Non-response rate	
George	2023	case-control	*	*	*	*	**	*	*	Good
Hallas	2009	case control	*	*	*	*	**	*	*	Good
Li	2024	Nested Case control	*	*	*	*	**	*	*	Good
Kristensen	2019	nested case control	*	*	*	*	*	*	*	Good
Salminen	2016	case-control	*	*	*	*	**	*	*	Good
Stritzelberger	2020	Nested case control	N/A	High risk of bias, not the aim of the study and not all data shown						Poor
Tilhonen	2022	case-control	*	*	*	*	**	*	*	Good

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Table S13. Critical appraisal table for cohort studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star)				Comparibility of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Asgari	2017	retrospective cohort		*	*	*	**	*	*	*	Good
Lin	2018	retrospective cohort study	*	*	*	*	**	*	*		Good
Cohen	1998		*	*	*	*	**	*	*	*	Good
George	2019	restrospective cohort study	*	*	*	*	**	*	*		Good
Huang	2016	retrospective cohort study	*	*	*	*	**	*	*	*	Good
Kessing	2015	Cohort (population based study)	*		*	*	**	*	*		Good
Kessing	2024	Cohort (Population based)	*	*	*	*	**	*	*	*	Good
Martinsson	2016	Cohort nationwide		*	*	*	**	*	*	*	Good
Zaidan	2014	retrospective cohort study	N/A - Data from cohort compared to general population, expressed as standardized incidence ratio; small cohort								Poor

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Table S14. Critical appraisal table for case-control studies on the use of lithium

Author	Year	Type of study	Selection (max 1 star) Comparability				Comparability (Max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Hallas	2009	case control	*	*		*		*	*	Poor
Kahan	2018	Case-control study from large database	Data from large database, scale non-applicable, high risk of bias							Poor
Li	2024	Nested Case control	*	*	*	*	**	*	*	Good
Pottengard	2016 (1)	Nationwide case control study	*	*	*	*	**	*	*	Poor
Pottengard	2016 (2)	Case control study nationwide	*	*	*	*	**	*	*	Good
Tamim	2008	Nested case-control	*	*	*	*	Lithium not main question of study	*	*	Poor

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Table S15. Critical appraisal table for cohort studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representatitveness 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	Adequace of follow up	
Moller	1989	Cohort	No control, high risk of bias								Poor
Rossing	2000	Retrospective cohort study	*	*		*	**	*	*	*	Good
Velicer	2006	Cohort study		*		*	**	*	*	*	Fair

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Table S16. Critical appraisal table for surveillance and case-control studies on the use of cimetidine

Author	Year	Type of study	Selection (max 1 star)				Comparibility (Max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of outcome	Non-response rate	
Colin Jones	1985	case control study	No representative outcome; already had gastrcic ulcers, only age and sex matched cont							Poor
Colin Jones	1991	surveillance study	No control, N/A							N/A
Coogan	2005	Database study/case-control	*		*		**			Poor
Holly	1997	population-based case-control study				*	**	*		Poor
Mathes	2008	Population based case-control study	*	*	*	*	**	*		Good
Moller	1992	Case-control study	High risk of bias							Poor
Schumacher	1990	Case-control study	*	*			**			Poor

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Table S17. Critical appraisal table for cohort studies on the use of haloperidol, clozapine, and olanzapine

Author	Year	Type of study	Selection (max 1 star)				Comparability of cohorts (max 2 stars)	Outcome (max 1 star)			Verdict
			Representativeness 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	Adequace of follow up	
Tilhonen	2022	cohort study	*	*	*	**	*	*	*		Good
Wang	2002	Retrospective cohort	*		*	*	*	*	*	*	Good

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Table S18. Critical appraisal table for case-control studies on the use of haloperidol, clozapine, and olanzapine

Author	Year	Type of study	Selection (max 1 star)				Comparibility (max 2 stars)	Outcome (max 1 star)		Verdict
			Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparibility of cases and controls	Ascertainment of outcome	Non-response rate	
Brainerd	2024	Case Control study	*	*	*	*	**	*	*	Good
Chen	2022	Case-control study	*	*	*	*	**	*	*	Good
Friedman	2020	Case-control	*	*	*	*	**	*	*	Good
Hsieh	2005	Database study/case-control	Scale not fully applicable due to study design, high risk of bia							Poor; N/A
Pottengard	1997	population-based case-control study	*	*	*	*	**	*	*	Good
Tiihonen	1990	Case-control study	*	*	*	*	**	*	*	Good

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