BIPOLAR DISORDER TREATMENTS AND OVARIAN CANCER: A SYSTEMATIC REVIEW

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Objective: We reviewed literature on drugs for bipolar disorders (BD), utilized in ovarian cancer (OC).

Method: We adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines in completion of this systematic review.

Results: We identified 73 papers. Thirty-two studies were finally included. BD is rarely diagnosed in OC patients. Limited finding from case reports is available. Drugs used to treat BD (mainly lithium and valproic acid) have been extensively studied in add-on to chemotherapy for treatment-resistant OC cells or in animal models, with promising results in vitro but not in vivo.

Conclusions: The clinical underestimation of BD in OC has leaded to the almost complete absence of evidences for a soundly based clinical guidance in this field. There is a urgent need for a systematic multi-disciplinary approach to OC.

Key words: bipolar disorders, ovarian cancer, mood stabilizers, atypical neuroleptics, psychopharmacology

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Introduction

Rationale

Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women in the world, accounting for an estimated 239,000 new cases and 152,000 deaths worldwide annually. The highest rates (11.4 per 100,000 and 6.0 per 100,000, respectively) are seen in Eastern and Central Europe (Reid, et al., 2017). A relevant percentage of women present with advanced stages of OC and are treated with surgery followed by chemotherapy. Despite improvements in chemotherapy, more than 80% of patients with advanced forms of OC might recur or develop drug resistance (Armstrong, et al., 2006). The OC diagnosis is affecting quality of life (QoL) and is often related to the occurrence of comorbid anxiety and depressive symptoms, as demonstrated by a number of studies, including a recent review and meta-analysis on depression in patients with OC (Watts, Prescott, Mason, McLeod, & Lewith, 2015). Several studies have been conducted on the potential correlations between antidepressants and the risk to develop OC, with the use of selective serotonin reuptake inhibitors (SSRIs) associated with a decreased risk of epithelial ovarian cancer, thereby implying potential chemo-preventive properties of these drugs (Mørch, Dehlendorff, Baandrup, Friis, & Kjaer, 2017). In all these studies, the manifestations of depression belong to the unipolar realm. Bipolar depression and mania/hypomania or mixed episodes seem to be virtually absent in OC patients. In some cases, Bipolar Disorder is an exclusion criterion, as reported, for example, in the clinical trial NCT00515372 ('*Depression Treatment and Screening in Ovarian Cancer Patients*', Anderson Cancer Centre, 2007-2019) (ClinicalTrials.gov 2019). As a consequence, no systematic information is provided on treatment options for OC patients with Bipolar Disorders, except for sporadic observations, such as case reports (Puangthong & Pongpirul, 2015; Pakhre, Krishnan, Pattanayak, & Khandelwal, 2016). The only syndrome that has been explored in a more systematic way in OC patients is the teratoma-associated anti-NMDAR encephalitis, that might occur with manic-like symptoms, such as agitation, excitement, speech confusion, behavioural problems, often misdiagnosed as *'acute psychoses'*, but not belonging to the psychopathological area of mood disorders (Koksal,

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Baybas, Mutluay, Altunkaynak, & Keskek, 2015).

Conversely, there is growing evidence on the clinical usefulness of a number of drugs commonly used to treat bipolar disorders, for example lithium and valproic acid (VPA), as add-on to the usual chemotherapy for treatment-resistant OC, leading to a paradox: there are no studies on the comorbidity between bipolar disorders and OC, and no indication on treatment choices is provided by literature, but a number of studies on OC (mainly cells or animal models) have been conducted using drugs commonly administered in patients with Bipolar Disorders, in add-on to standard chemotherapies for treatment-resistant OC.

Objectives

The main aim of this paper is to systematically review finding on the use of the most common drugs utilized for the treatment of Bipolar Disorders when administered in OC. We started from two lines of evidence: 1) there are no studies on the treatment of Bipolar Disorders in OC patients; 2) there are studies on drugs commonly utilized to treat bipolar disorders that have been utilized to treat OC, but with rationales other than the treatment of bipolar signs and symptoms. We would like to explore if these studies could be in some way useful to provide information for a treatment algorithm of bipolar disorders when occurring in OC patients.

We set out to systematically review the published literature on the topic in accordance with the PICOS process as follows: P—population: female patients of any age who met the diagnosis criteria for ovarian cancer (OC), at any stage; I—intervention: administration of drugs commonly used for the treatment of bipolar disorders; C—comparison: patients with OC before and after treatment with such drugs, and matched groups or control groups (when available); O—outcome: changes in OC prognosis, however expressed (absolute value, z- or t-scores standard deviations, increases in percentage from baseline to follow-up); S—study design: we initially included randomized controlled trials (RCTs), cohort studies, case–control studies, follow-up studies, pilot studies, quasi- experimental studies, case series, or case reports. However, we decided to perform the systematic review on all studies we retrieved, considering that no randomized controlled trials (RCTs) have been performed.

Materials and methods

We adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines in completion of this systematic review (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2010).

Protocol and registration

This systematic review is not included in a research protocol.

Eligibility criteria

We proceeded using the following criteria: all studies published between 1988 and January 2019 using PubMed were included, provided that they met the following criteria: 1) written in English; 2) original articles on studies with a longitudinal design; and 3) prospective or retrospective, observational (analytical or descriptive), experimental or quasi-experimental, controlled or non-controlled studies, case reports or case series. Reviews and non-original articles (ie, Letters to the Editor, and book chapters) were not included.

Information source and search strategy

The literature search was designed and performed independently in duplicate by two authors. No studies were retrieved combining [Bipolar Disorder] AND [Ovarian Cancer], nor [mania] or [manic episode] AND [Ovarian Cancer], nor [hypomania] or [hypomanic episode] AND [Ovarian Cancer], nor [bipolar depression] AND [Ovarian Cancer], nor [mixed episode] AND [Ovarian Cancer]. The PubMed database was then systematically screened using the following terms: [Lithium] AND [Ovarian Cancer] (n=33); [Valproate] AND [Ovarian Cancer] (n=30); [Carbamazepine] and [Ovarian Cancer] (n=4); [Olanzapine] AND [Ovarian Cancer] (n=4); [Risperidone] AND [Ovarian Cancer] (n=1); [Clozapine] AND [Ovarian Cancer] (n=1). Again, no studies were found combining [Lamotrigine], [Oxcarbazepine], [Aripiprazole], [Quetiapine], [Paliperidone] AND [Ovarian Cancer], leading to a total of 73 papers. No additional records were selected after a manual search that was carried out to retrieve other articles that had not been previously identified.

Study selection

Two authors independently screened the resulting articles for their methodology and appropriateness for inclusion. Non-controlled studies as well as studies that did not consider treatment response as primary outcome were excluded from the systematic review and summarized in **table 1**. Quality appraisal of controlled studies was conducted according to the RCT of. Consensus discussion was used to resolve disagreements between reviewers.

Data collection process and data items

First, two independent authors for language suitability and subject matter relevance assessed the title and abstract of each paper, and the studies thereby selected were assessed for their appropriateness for inclusion and quality of method. The first author, year of publication, design, sample age, duration of follow-up, intervention, and main findings are summarized in **table 1**.

Risk of bias in individual studies

Not applicable

Data synthesis

Due to the lack of homogeneity among the resulting studies, a meta-analysis could not be performed. In particular, studies varied in designs and in terms of how improvements were measured. Hence, this systematic review is presented as a narrative synthesis.

Table 1. *Summary of Evidence on Drugs for Bipolar Disorders in Patients with Ovarian Cancer*

Author	Sample	Methods and Rationale	Results
Studies on Valproate			
Booth, Roberts, Rais, Poklepovic, & Dent 2018	OC cells	VPA in add-on to niraparib to enhance its lethality. VPA and niraparib interacted to cause greater levels of autophagosome and subsequent autolysosome formation in OC cells and in athymic mice.	OC cells expressing mutant RAS were associated with a weaker response to chemotherapy and a shorter overall patient survival. In vivo VPA+palbociclib and neratinib+VPA+palbociclib interacted to suppress the growth of a carboplatin/paclitaxel resistant PDX tumors expressing a mutant N-RAS.
Booth et al., 2018	OC cells of a patient donor, completely chemotherapy resistant	Neratinib down-regulate the expression of epidermal growth factor receptors (EGFR, HER1, ERBB1), biomarkers for tumor cell growth, invasion and resistance to chemotherapy. Neratinib could also down-regulate other plasma membrane proteins, as the proto- oncogene RAS.	Neratinib and the HDAC inhibitor VPA interacted to kill ovarian carcinoma cells in a greater than additive fashion, reducing the N-RAS level
Booth et al., 2019	OC cells	Combined treatment of neratinib (irreversibile inhibitor of ERBB 1/2/4), palbociclib (CDK 4/6 inhibitor), sildenafil (PDE5 inhibitor) and VPA (HDAC inhibitor).	Neratinib and palbociclib interacted in a greater than additive manner to increase autophagosome and then autolysosome levels in a time dependent fashion, and to cause tumor cell killing. The lethality of neratinib+palbociclib was modestly enhanced by sildenafil and strongly enhanced by VPA.
Xiong et al., 2018	Selection of the Kyoto Encyclopedia of Genes and Genomes and Reactome pathways for overlapped genes.	Connectivity map analysis to identify treatment options for ovarian serous cystadenocarcinoma with the Network pharmacology method. Identification of the intersections between the ovarian serous cystadenocarcinoma-related genes and the compound targets. Selection of the Kyoto Encyclopedia of Genes and Genomes and Reactome pathways of the overlapped genes. Construction of a correspondence compound-target pathway network.	Identification of 541 ovarian serous cystadenocarcinoma-related genes, associated critical tumor-related pathways. Five compounds (including VPA) as treatment agents for ovarian serous cystadenocarcinoma, with 48 targets. Following the 48 targets, six (PTGS1, FOS, HMOX1, CASP9, PPARG, ABCB1) were selected as therapeutic targets by the five compounds with synergistic anti-ovarian serous cystadenocarcinoma potential.
Sajadpoor et al., 2018	OC cells (A2780/CP). SiRNA Transfection (H19 siRNA (si-H19) or scrambled (control)	VPA treatment effect on H19 (a lncRNA involving in cisplatin resistance in cancers) expression in OC cells. Relation of the H19 levels with apoptosis and cisplatin resistance.	VPA led to significant increase in apoptosis rate, and increased the cisplatin sensitivity of A2780/CP cells. Decrease of the expression of H19 and EZH2 proteins; increase of the expression of p21 and PTEN. H19 was inhibited by a specific siRNA. H19 knockdown by siRNA induced apoptosis and sensitized the A2780/CP cells to cisplatin-induced cytotoxicity. VPA negatively regulates the expression of H19 in ovarian cancer cells, which subsequently leads to apoptosis induction, cell proliferation inhibition, and overwhelming to cisplatin resistance.
Motamedian, Taheri, & Bagheri, 2017	OC cells	Screening of the Drugbank database. A set of metabolic models specific for the NCI-60 cell lines was developed (GSE5846). Mean expression of genes in 5 replicates for resistant and sensitive cells (GSE15709) was used to reconstruct cisplatin-resistant and -sensitive A2780 epithelial OC models.	The concentration of each drug (in combination with cisplatin) that resulted in a 20% death rate in cisplatin-resistant cells was determined. Nine drugs were used, namely aciclovir, azathioprine, terbinafine, capecitabine, hyralazine, nitisinone, orlistat, VPA and vigabatrin in addition to cisplatin. Azathioprine, terbinafine, hydralazine and VPA were effective against the proliferation rates of resistant cells with cell viability of 47%, 54%, 44% and 72%

Table 1. *Continued*

Author	Sample	Methods and Rationale	Results
Studies on Valproate			
Booth, Roberts, Poklepovic, & Dent, 2017	OC cells and non-small cell lung cancer (NSCLC).	Continuation of earlier work combining pemetrexed+sildenafil; analyses with the multi-kinase and chaperone inhibitor pazopanib with the histone deacetylase inhibitor AR42.	Pemetrexed+sildenafil reduced the expression of multiple histone deacetylase proteins in lung and OC cells within 6h. AR42 and VPA both enhanced the lethality of pemetrexed+sildenafil against NSCLC cells as well as OC cells.
Ravera et al., 2017	Cisplatin-sensitive OC cells A2780	OC cells A2780 challenged with cationic liposomes containing the single drug cisplatin or VPA or their combination with an approximate 1 : 2 molar ratio.	VPA barely penetrates cells unless it is transported by liposomes or it is coordinated to a lipophilic assembly. Cisplatin is the more potent antiproliferative agent, but the two drugs have a synergistic action.
Štarha, Trávníček, Křikavová, & Dvořák, 2016	A2780 OC cells	Organometallic Ru(II) half-sandwich complexes with in vitro cytotoxicity. To study the replacement of the chlorido ligand with other halogenido ligands as well as by the VPA and PB ligands.	In vitro cytotoxicity is improved when the chlorido ligand is replaced by different halogenido ligand. Platinum, VPA, and 4 phenylbutyrato (PB) complexes exhibited higher in vitro cytotoxicity than their hydroxidoplatinum analogues. Complexes were in vitro inactive against the A2780 OC cell lines, up to the highest tested concentrations.
Kwiecinska et al., 2016	OC cells (OVCAR-3, TOV-21G, and TOV-112D)	Assessment of cell viability (XTT assay), caspase-3 activity, and expression of cell cycle-and apoptosis-related genes and proteins, when treated with chemotherapic alone or combined with VPA. Effects on α-tubulin acetylation and DNA fragmentation.	VPA co-treatment enhanced paclitaxel and doxorubicin effects in decreasing cell viability and in increasing caspase-3 activity. No effect with carboplatin and cyclophosphamide. Effect of the combined treatment with paclitaxel, doxorubicina and VPA on gene expression (increased expression of CDKN1A, CCNE1, PARP1, PARP3). VPA co-treatment enhanced paclitaxel and doxorubicin effects on protein expressions. VPA did not increase paclitaxel-induced α-tubulin acetylation.
Kwiecińska, Wróbel, Taubøll, & Gregoraszczuk, 2014	OC cells (OVCAR-3)	To compare the effects of VPA and levetiracetam as Histone deacetylases Inhibitors (HDACIs).	OVCAR-3 cells were cultured with VPA or LEV at concentrations between 1 and 10 mM for 1-24 h. VPA produced a concentration and time-dependent decrease in HDAC activity in OVCAR-3 cells accompanied by histone hyperacetylation. LEV had no effect on HDAC activity, or gene and protein expression.
Li et al., 2013	Nine cancer cell lines (ovarian, cervical, endometrial, uterine)	To investigate if VPA and Aurora kinase inhibitor VE465 may have additive/synergistic effects on gynecologic cells.	Combined VPA and VE465 enhanced cytotoxic effect on some gynecologic cancer cells. The possible mechanisms may be achieved via induction of apoptosis.
Song et al., 2013	OC cells	Adoptive transfer of autologous tumor-infiltrating lymphocytes (TILs) is a therapy for OC, still limited in the identification and expansion of tumor-reactive TILs. A rapid generation of tumor antigen-specific T cells is through the genetic modification of nonreactive T cells to express a chimeric antigen receptor (CAR). The incorporation of co-stimulatory signaling domains in a folate receptor-α. FR-specific CAR may improve persistence/antitumor activity of transferred CAR T cells.	NKG2D ligands (NKG2DLs) comprise two members of the MIC (MHC class I-related chain) family and six members of the ULBP/RAET (UL16-binding protein, or retinoic acid early transcript) family, generally absent or expressed at low levels by healthy tissues but widely expressed on OC. A novel NKG2DL-specific CAR containing the extracellular domain of the NKG2D receptor, to allow its recognition of ligands on the cancer cell surface was constructed. Pretreatment of OC cells expressing moderate to low levels of NKG2DLs with valproate upregulated NKG2DL cell surface expression and enhanced immune recognition by chimeric NKG2D CAR T cells.
Shan, Feng-Nian, Jie, & Ting, 2012	OC cells (SKOV3) and human OC model subcutaneous in mice.	To define the biological therapeutic effects of valproate in the treatment of OC in vitro and in vivo. Valproate was dissolved in phosphate-buffered saline (PBS) at concentration of 1, 2, 3, 4,5mmol/L.	Effect on cellular morphology of SKOV3 cells with VPA >= 3 mmol/L: cells growth inhibited and normal cells dropped off. With VPA concentration between 3 to 5 mmol/L, the growth of SKOV3 cells was inhibited. The inhibiting rates of VPA vs dichloroplatinum (DDP) vs. VPA+DDP group were 40.7%, 45.3%, 58%, significantly higher than controls
Kwiecińska, Taubøll, & Gregoraszczuk, 2012a	OC cells (OVCAR-3)	To compare the effect of VPA and levetiracetam on apoptotic mechanisms including gene and protein expression in e OVCAR-3. Cells were cultured with VPA or levetiracetam at concentrations between 0.1 mM and 10 mM (apoptosis assessed by DNA fragmentation assay).	VPA at concentrations > 5 mM produced an increase in DNA fragmentation. Exposure to levetiracetam did not affect DNA fragmentation or the modulation of the mechanisms of apoptosis.

Table 1. *Continued*

Author	Sample	Methods and Rationale	Results
Studies on Valproate			
Kwiecińska, Taubøll, & Gregoraszczuk, 2012b	OC cells (OVCAR-3)	To compare the effect of valproate and levetiracetam on proliferation, cytotoxicity and expression of cell cycle regulatory genes in the human OC cell line OVCAR-3. Cells were cultured with VPA or levetiracetam at concentrations between 0.1 mM and 10 mM.	Levetiracetam disrupts cells metabolism, but has no effect on cell proliferation and cell cycle regulating genes expression.
Yan & Zhang, 2012	Oc cells (HO8910) 20 female BALB/c nude mice 4-6weeks old.	To compare the effect of valproate at different concentrations on HO8910 cells (experimental vs control group) Moreover, trypsinized HO8910 cells suspension (2×106/ml) was subcutaneously injected per mouse at right forelimb.	Significant decrease (P <0.05) in cell proliferation in the experimental groups than in the control group (p=0.032). Cells treated with increasing concentrations of VPA showed markedly morphological changes. A significantly higher number of cells in the experimental groups with various doses of VPA (1.0, 2.0, 3.0 and 4.0mmol/L respectively) were blocked at G0/G1 phase, compared with the control group (P <0.05). All apoptotic rates in the experimental groups from low to high doses of VPA were statistically and gradually higher (P <0.05) as compared to the control group. The expression levels of WWOX and P27 in the experimental groups were significantly and gradually increased (P <0.05) compared with control group. The average tumor size of the experimental group (fed on VPA solution) was significantly lesser (1264.59±24.83 vs. 2155.62±73.38mm3, P <0.05) than control group. The average survival time was significantly higher in the experimental group (47.12±0.73 vs. 34.58±0.46 days, P <0.05) vs. control group.
Lin et al., 2008	OC cells (SK-OV-3, OVCAR-3, and TOV-21G).	To test whether valproate, as HDAC inhibitor could result in synergistic cytotoxicity with cisplatin in OC cells lines with various sensitivities to cisplatin.	VPA not only exhibited synergistic cytotoxicity with cisplatin in all of the OC cells tested, but also re-sensitized the cells that acquired cisplatin resistance. Reactive oxygen species accumulation and tumor suppressor phosphatase and tensin homolog (PTEN) over-expression, up-regulated by VPA, contributed to the enhanced cytotoxicity.
Candelaria et al., 2007	Phase II, single-arm study on pts with cervix (n=3), breast (n=3), lung (n=1), testis (n=1), and OC (n=7).	Hydralazine and VPA in add-on to chemotherapy with cisplatin, carboplatin, paclitaxel, vinorelbine, gemcitabine, pemetrexed, topotecan, doxorubicin, cyclophosphamide, and anastrozole. Patients were >18 ys, receiving their 2nd, 3rd, or 4th line of palliative chemotherapy. They showed at the second or third chemotherapy course progressive disease as their maximum response according to Response Evaluation Criteria in Solid Tumors (RECIST), or Gynecologic Cancer Intergroup (GICG) CA125 criteria (in the case of patients with OC). Patients received hydralazine at 182 mg for rapid, or 83 mg for slow, acetylators, and VPA at 40 mg/kg, starting a week before chemotherapy.	Evaluation of response, toxicity, DNA methylation, histone deacetylase activity, plasma valproic acid, and hydralazine levels.Clinical benefit was observed in 12 (80%) of the 15 patients. Four had a partial response (PR) and 8 a stable disease (SD). Among PR, 3 were in OC according to IGCG CA125 criteria. Regarding patients with SD, 4 occurred in patients with OC and one each in patients with cervix, lung, testis, and breast cancer.
Takai et al., 2004	OC cell lines (SK-OV-3, OVCAR-3, TOV-21G, OV-90, and TOV-112D). Ten 6-week-old immunodeficient beige/nude/xid nu/nu female mice.	To define the biologic and therapeutic effects of histone deacetylase inhibitors (HDACIs) including valproate,in the treatment of OC. To test the ability of valproate to inhibit the growth of the OC cell line SK-OV-3 in vivo.	All OC cell lines were sensitive to the growth-inhibitory effects of the HDACIs. Cell cycle analysis indicated that their exposure to HDACIs decreased the proportion of cells in S phase and increased the proportion of cells in the G0/G1, and or G2/M phase. HDACIs induced apoptosis, with alterations in the expression of genes related to apoptosis, cell growth, and phenotype, including the activation of caspase-9 and caspase-3. Valproate in mice significantly inhibited human OC growth without toxic side effects.

Table 1. *Continued*

Author	Sample	Methods and Rationale	Results
Studies on Carbamazepine			
Toffoli et al., 2000	OC cells, solid tumors, normal ovarian cells	Human OC cell lines SKOV-3 were chronically exposed in vitro to CBZ (50 and 100 □g/ml CBZ concentrations). A selection of the SKOV-CBZ clones more resistant to MTX was made.	SKOV-CBZ clones developed resistance towards MTX due to defective MTX uptake. CBZ altered the intracellular transport of folates.
Studies on Olanzapine and Risperidone			
Sanomachi et al., 2017	OC cells	OLZ alone or in combination with chemotherapeutic agents, on survivin expression and cell viability as investigated in OC cell lines.	OLZ reduced survivin expression and chemo-sensitized serum-cultured non-CSC ovarian cancer cells that expressed survivin.
Puangthong & Pongpirul, 2015	Case Report on a female pt with psychosis	A 25-year-old woman with ovarian germ cell tumour and behavioral changes after receiving an intensive dose of neo-adjuvant chemotherapy with bleomycin, etoposide and cisplatin, for an OC relapse.	Pt with flights of ideas and hyperactivity, paranoid ideations, auditory hallucinations, and thoughts of being wealthy (Psychotic Disorder NOS). She received an incremental dosage of olanzapine from 5 to 20 mg/day with no control of psychotic symptoms during the first week; she was switched to risperidone. Symptoms were controlled at 4 mg/day of risperidone.
Studies on Clozapine			
Pakhre, Krishnan, Pattanayak, & Khandelwal, 2016	Case Report on a female pt with psychosis	38-year-old female, with OCD, and bipolar affective disorder treatment-resistant, administered with clozapine (200-300 mg/day) in add-on to lithium (900 mg/day) and lamotrigine. OC diagnosis (papillary adenocarcinoma Stage IIIC). Surgery and chemotherapy with carboplatin. CLZ discontinued.	Two weeks after clozapine cessation, the patient had manic symptoms. As the patient had not shown response to haloperidol for optimum dose and duration, clozapine was reintroduced in addition to lithium and lamotrigine, despite the potential side effects on blood count.
Studies on Lithium			
Mathuram, Ravikumar, Reece, Sasikumar, & Cherian, 2017	TeratoCA derived OC PA-1 cells	GSK-3 inhibitors as viable apoptotic inducers. MTT assay was carried out to assess inhibitory concentrations of LiCl and TDG. AO/EB staining and Hoechst 33258 staining were employed to assess the damage	Protein expression of caspase-3 caspase-7, caspase-9, PARP exhibited significant cleavage in LiCl and TDG-treated cells. Protein expression of Cox-2 was significantly increased in IC50 concentration of TDG. Cell cycle analysis showed significant accumulation of cells at sub-G0-G1.
Ozretic et al., 2017	Twenty-three samples of OC vs tissues from 9 healthy ovaries (OV) and 9 healthy fallopian tubes (FT) excised for other reasons	Primary cells developed from OC tissues respond to cyclopamine treatment with a short-term decrease in cell proliferation, downregulation of Hedgehog pathway genes, including BIRC5, and changes in protein dynamics. Stimulation with SHH protein results in increased cell migration, while GLI1 transfection or PTCH1 silencing demonstrate pathway upregulation. LiCl at the GSK3β-SUFU-GLI level can modulate the pathway activity, thus suggesting at least partial non-canonical activation.	Cells treated with 7.5 μM cyclopamine, 3 ng/μl SHH protein for 96 h, 2.5 and 5 μM GANT-61 or 5 and 10 mM lithium chloride (LiCl, Kemika) for 48 h. For MTT assay, primary cells or SKOV-3 cells were plated in 96-well plates, and treated the following day. Cell proliferation was measured after 24, 48 and 72h. After treatment with LiCl a decrease in the levels of GLI3 activator form (GLI3A) can be noted in both cell lines. The GLI3 repressor form (GLI3R) was undetectable under these conditions in the SKOV-3 cell line, but in the primary cell line an increase in GLI3R levels can be observed after treatment with 10 mM LiCl. Levels of PTCH1, a marker of Hedgehog pathway activity, are decreased in both cell lines after LiCl treatment, indicating signaling down-regulation. Both cell lines showed down-regulated Hedgehog signaling, after LiCl treatment, indicated by decreased PTCH1 protein levels

Table 1. *Continued*

Author	Sample	Rationale	Results
Studies on Lithium			
Mitra & Roy, 2017	OC adenocarcinoma cells SK-OV3 and OAW-42	Hyperactivation of the TGFβ pathway has been reported as playing a role in later stages of OC by inducing Epithelial-Mesenchymal Transition (EMT).	EMT was reduced when OC cells were co-activated with TGFB1 and LiCl
Fu et al., 2014	71 patients with epithelial ovarian cancer (EOC) 20 samples of benign ovarian tumor In vivo, xenograft mice	Glycogen synthase kinase-3 (GSK-3) plays an important role in human cancer. The aim of this study is to evaluate the clinicopathological significance of expression of GSK- 3α/β and pGSK-3α/β$^{Tyr279/216}$ in patients with epithelial OC to investigate whether GSK-3 inhibition can influence cell viability and OC tumor growth. Two GSK-3 inhibitors, lithium chloride (LiCl) and 4-benzyl-2-methyl-1,2,4- thiadiazolidine-3,5-dione (TDZD-8), were used.	Both LiCl and TDZD-8 can decrease cell viability of SKOV3 and SKOV3-TR30. To determine whether GSK-3 inhibition affects ovarian tumor growth in vivo, a xenograft model of OC generated by SKOV3 cells was used. Tumor growth was slowed in the LiCl group also in animal model
Novetsky et al., 2013	Two OC cells (SKOV3 and OVCA 433). Primary cultures collected from patients with metastatic high-grade serous ovarian cancer	LiCl has anti-cancer properties at supra-therapeutic doses. This study was designed to determine whether LiCl, as a single agent or in combination with cytotoxic agents reduces OC cells growth and metabolic activity at clinically achievable levels.	LiCl on metabolic activity Metabolic activity was significantly reduced in the OVCA 433 and SKOV3 cells lines after treatment for 96 hours with 10mM LiCl (83% and 63% reduction, respectively) as measured by MTT assays (Figure 2A). The effect was evident as early as 48 hours after treatment and showed clear cell density effects, with the greatest inhibition seen with rapidly proliferating, subconfluent cultures (data not shown). Treatment with 1mM LiCl resulted in no change in metabolic activity in either cell line LiCl effects in primary ovarian cancer cultures Overall, three of the six primary cultures (WUOVCa1-3) showed a significant combinatorial effect with 1mM LiCl and either cisplatin or paclitaxel with an additional 5-8% absolute decrease in their relative metabolic activity from treatment with a single agent. The remaining three primary cultures (WUOVCa4-6) displayed no combinatorial effect LiCl effects on cellular proliferation and clonogenic potential Lithium chloride, as a single agent or in combination with cytotoxics had limited effect on clonogenic potential.
Cai, Wang, Xin X, Ke, & Luo, 2007	Human ovarian epithelial adeno-carcinoma cell lines (A2780 and CP70)	This is the first report revealing a potential role of GSK-3ß in cisplatin resistance of ovarian carcinomas.	Increased expression of pGSK-3ß- ser-9 in cisplatin-resistant CP70 cells compared to their cisplatin-sensitive counterpart A2780 cells. High pGSK-3ß- ser-9 levels in CP70 cells suggesting that a suppressed GSK-3ß activity may account for their resistance to cisplatin. LiCl, a GSK-3ß inhibitor significantly raises the IC of cisplatin for both OC cells
Cao, Lu, & Feng, 2006	SKOV3 and ES-2 cells. + Female mice aged 3-4 weeks	To assess whether GSK-3β affects the proliferation of OC cells, the effect of LiCl, a known inhibitor of GSK-3, was investigated on the growth of two human ovarian tumor cell lines, SKOV3 and ES-2 and in animal models.	After 48 and 72 h of treatment, the growth of the cells was significantly inhibited by LiCl LiCl inhibited ovarian cancer growth in animal models

Results

We found a total of 73 records (**figure 1**). Forty-one records were excluded (41/73=56.1%), because not pertinent to the selected topics (37/73=50.6%), or reviews (1/73=1.3%) or not written in English (2/73=2.6%); one was a duplicated record (1/73=1.3%). Finally, 32 studies (32/73; 43.8%) were included in the review, as summarized in **table 1**.

Summary of evidence

Lithium in Ovarian Cancer

Lithium is the most important mood stabilizer, with a number of studies on its efficacy on both depressive and manic episodes of Bipolar Disorder and on the long-term prophylaxis of relapses and recurrences (Goodwin & Consensus Group of the British Association of Psychopharmacology, 2009). The potential relationships between the long-term treatment with lithium and the risk for some forms of cancer (urinary tract and thyroid cancer) have been extensively explored, leading to controversial results (Ozerdem, Ceylan, & Targıtay, 2009). The overall incidence and mortality rates of cancer in patients with Bipolar Disorders are higher when compared with the general population, but growing evidence identifies a protective effect of LiCl on cancer proliferation through the inhibition of glycogen synthase kinase-3β (GSK-3β), the modulations of redox status, inflammatory changes, pro-/anti-apoptotic mechanisms, and mitochondrial functions (Ozerdem, Ceylan, & Targıtay, 2009). A recent population-based cohort study investigated the association between lithium and overall cancer risk in patients with bipolar disorders (Huang, Hsieh, Huang, & Yang, 2016). Study participants who have been diagnosed with Bipolar Disorder were extracted from a database collected during a decade (1998-2009), with the exclusion of patients who received a cancer diagnosis prior to index drug use, and of patients who never used lithium or anticonvulsants. Patients were then divided into three groups: anticonvulsants only, lithium only and ever exposure to lithium/anticonvulsants. Compared with anticonvulsants only exposure, lithium exposure was associated with significantly lower cancer risk (HR=0.735, 95% CI 0.554-0.974) with a dose-response relationship.

The LiCl inhibition of the serine/threonine protein kinase 3β (GSK3β) has been found to play an important role in OC cellular metabolism, transcription, cell cycle division, apoptosis and maintenance of stem cells (Wang et al., 2008). Phosphorylation of β-catenin by GSK3β leads to growth arrest (Woodgett, 1994). Conversely, GSK3β may activate NFκB dependent gene transcription, leading to cellular proliferation and survival. Lithium chloride (LiCl) inhibits GSK3β through two mechanisms: it competes with magnesium to bind to GSK3β and disrupts its catalytic function due to its lower charge density (Ryves & Harwood, 2001) Additionally, LiCl has been associated with phosphorylation of a regulatory serine-9 on the N-terminal region, which is a principal regulator of GSK3β (Li et al., 2007).

In vitro studies demonstrated that LiCl could inhibit growth of endometrial cancers and OC (Cao, Lu, & Feng, 2006). However, LiCl has been utilized at supra-physiologic doses, thus limiting the applicability to in vivo models. Therapeutic serum levels for lithium chloride are 0.8-1.2meq/L (0.8-1.2mM) with lithium toxicity usually beginning at 1.5-2meq/L (1.5-2mM) (Novetsky et al., 2013). In a recent study lithium chloride, as a single agent or in combination with cytotoxic agents, has been tested on ovarian cancer cells growth and metabolic activity at clinically achievable levels, namely 1mM. Two high-grade serous ovarian cancer cell lines were utilized, SKOV3 and OVCA 433. Unfortunately, treatment with 1mM LiCl had no effect on the cell cycle distribution or metabolic activity. The combined treatment with cisplatin or paclitaxel led to statistically significant decreases in metabolic activity in the OVCA 433 cell line and 50% of cultures investigated. The decreased metabolic activity was not associated with decreased cell growth or clonogenic potential. Lithium's effect seemed to be only on the disruption of cellular metabolism, with a limited clinical benefit. This finding confirmed a previous phase II trial of LiCl in low-grade neuroendocrine tumors that failed to demonstrate a clinical response (Lubner et al., 2011).

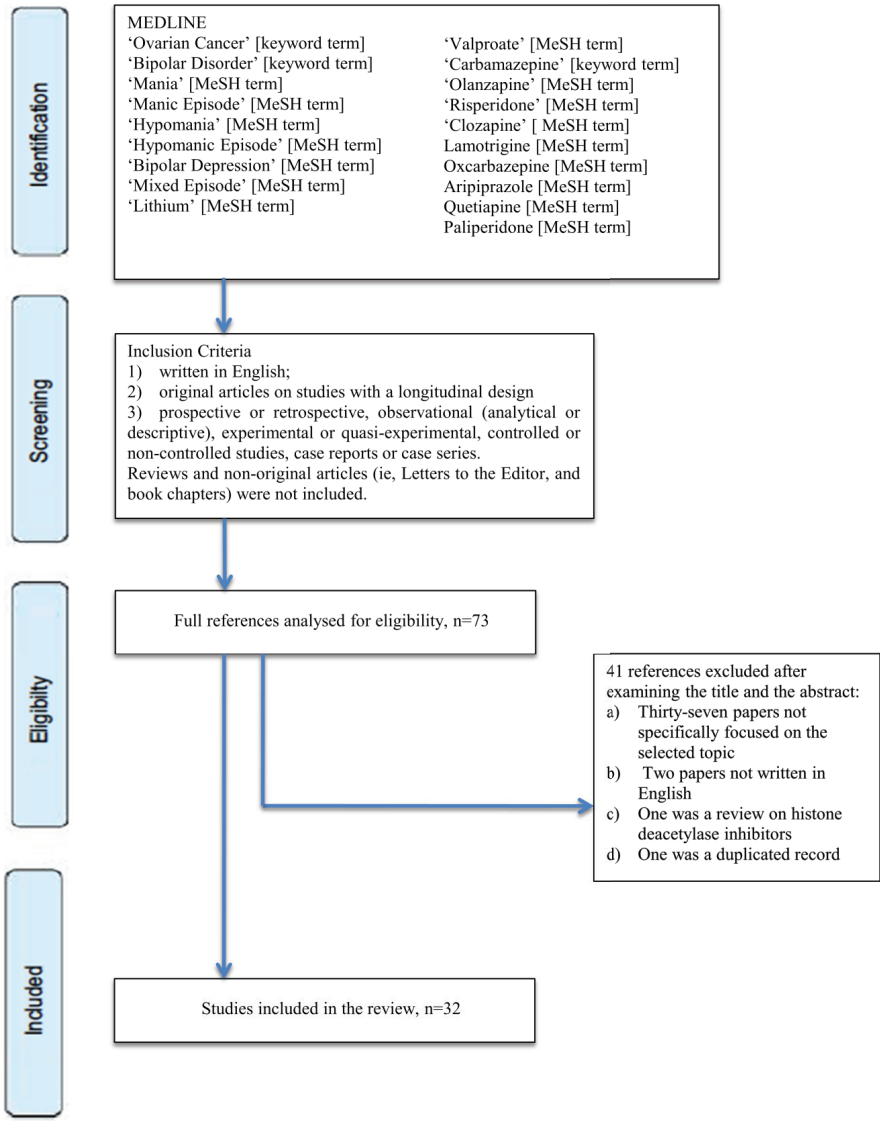
In summary, despite these limitations, lithium is still considered a *'viable treatment'* option for OC. It has been tested in a number of studies on OC cells, even if at supra-physiologic levels (for example, 25 mM), including the aggressive epithelial ovarian cancer cells (EOC) (Fu et al., 2014; Mitra & Roy, 2017). Treatment with lithium chloride has been shown to be effective by in vitro studies in OC cancer types. Unfortunately, in vivo studies are limited, and no clinical response at therapeutic dosages is present. These disparate results may be due to the supra-physiologic doses used in the pre-clinical studies, suggesting that LiCl, at physiologic levels, would be of limited clinical benefit in the treatment of OC.

Valproate in Ovarian Cancer

Valproate (VPA) is an effective drug employed in several neuropsychiatric diseases, including bipolar disorders. An increased prevalence of polycystic ovary syndrome (PCOS) associated with VPA has been reported in both women with epilepsy and women with bipolar disorders (Bilo & Meo, 2008). The risk of developing PCOS during VPA treatment seems to be higher in women with epilepsy than in women with bipolar disorders, and this might be due to an underlying neuro-endocrine dysfunction related to the seizure disorder (Okanović & Zivanović, 2016). Giving that, both psychiatrists and gynecologists are aware of the possibility that PCOS in these populations of patients might be related to VPA use. Thus, the long-term administration of VPA in women with bipolar disorder or epilepsy might result in the increased risk of hyperandrogenism, menstrual abnormalities and polycystic ovaries. VPA may also increase the risk of infertility and other associated symptoms of polycystic ovarian syndrome (Okanović & Zivanović, 2016). Therefore, particular caution is indicated in the use of VPA in women with Bipolar Disorder of reproductive age (Okanović & Zivanović, 2016). Conversely, VPA demonstrated, as histone deacetylase inhibitor (HDAC), anti-cancer properties in culture and animal studies on OC. VPA can facilitate the induction of autophagosome levels when combined with a variety of agents that cause DNA damage (pemetrexed) or might cause inhibition of protective signal transduction pathways (neratinib), thus enhancing the sensitivity of OC cells to a number of chemotherapeutic agents (Thotala et al., 2015).

Recent studies (Booth et al., 2018a; Booth et al., 2019) demonstrated the efficacy of the combination of neratinib and VPA, and of neratinib (15 mg/kg QD), palbociclib (5 mg/kg QD) and VPA (50 mg/kg QD) on carboplatin/paclitaxel resistant ovarian carcinoma cells.

Figure 1. *Preferred Reporting items for Systematic Review and Meta-Analyses (PRISMA) Flow Diagram of Studies' Selection*



Niraparib, that could modestly enhance autophagosome formation, has been combined with VPA, with positive results: the two compounds interacted to cause greater levels of autophagosome and subsequent autolysosome formation in OC cells (Booth, Roberts, Rais, Poklepovic, & Dent, 2018b). Previously, the same research group tested the combination pemetrexed + sildenafil to alter the immunogenicity of lung and OC cells. The pemetrexed + sildenafil lethality was enhanced both by the histone deacetylase inhibitors AR42 and VPA (Booth, Roberts, Poklepovic, & Dent, 2017). VPA has been also included in a list of five treatment agents (together with resveratrol, MG-132, puromycin, and 15-delta prostaglandin J2) in a study on ovarian serous cystadenocarcinoma (Xiong et al., 2018).

As already noticed, cisplatin resistance is one of the main limitations in the treatment of OC, which is partly mediated by long non-coding RNAs (lncRNAs). H19 is an lncRNA involving in cisplatin resistance in OC. VPA may display its effects through regulation of non-coding RNAs controlling gene expression. Sajadpoor et al. (2018) investigated VPA treatment effect on H19 expression in OC cells and also the relationship of H19 levels both with apoptosis and cisplatin resistance. VPA treatment not only produced a significant increase in apoptosis rate, but also increased the cisplatin sensitivity of A2780/CP cells. Motamedian, Taheri, and Bagheri (2017) obtained a similar result on the synergistic effect of VPA, azathioprine, terbinafine, and hydralazine with cisplatin, in a study that utilized an algorithm (Transcriptional regulated flux balance analysis, TRFBA) to identify genes affecting the growth of drug-resistant cancer cells.

VPA co-treatment with paclitaxel (PTX), doxorubicin (DOX), carboplatin (CBP) and cyclophosphamide (CP) has been applied to three different OC cell lines (OVCAR-3, TOV-21G, and TOV-112D) treated with the above-mentioned chemotherapeutic drugs, alone or in combination with VPA (Kwiecińska et al., 2016). The effects of these drugs on α-tubulin acetylation and DNA fragmentation were investigated. Results were non-univocal: paclitaxel and DOX decreased

cell viability and increased caspase-3 activity, and co-treatment with VPA enhanced this effect; carboplatin and CP had no effect. Responses to treatment with PAX and DOX together with VPA on gene expression profile were highly variable and depended on the cell line investigated. VPA did not increase PTX-induced α-tubulin acetylation. An additive effect of DOX with VPA on DNA fragmentation was observed in TOV-21G and TOV-112D cell lines but not in the OVCAR-3 (Kwiecińska et al., 2016).

Taken as a whole, studies were concordant in purposing VPA as a promising drug to achieve the goal of overcoming cisplatin resistance of OC in the future, and in supporting drug trials with this agent. Only one study is available with valproate in a group of 7 patients with resistant OC (Candelaria et al., 2007). This Phase II, single-arm study was conducted on a sample of patients with cervix (n=3), breast (n=3), lung (n=1), testis (n=1), and OC (n=7). Hydralazine and valproate were administered in add-on to chemotherapy with cisplatin, carboplatin, paclitaxel, vinorelbine, gemcitabine, pemetrexed, topotecan, doxorubicin, cyclophosphamide, and anastrozole. Patients were enrolled if receiving their 2nd, 3rd, or 4th line of palliative chemotherapy, and if they showed at the second or third chemotherapy course, progressive disease as their maximum response according to Response Evaluation Criteria in Solid Tumors (RECIST), or Gynecologic Cancer Intergroup (GICG) CA125 criteria (in the case of patients with OC). Patients received hydralazine at 182 mg for rapid, or 83 mg for slow, acetylators, and valproate at 40 mg/kg, starting a week before chemotherapy. Evaluation of response, toxicity, DNA methylation, histone deacetylase activity, plasma valproic acid, and hydralazine levels were considered. Clinical benefit was observed in 12 (80%) of the 15 patients. Four had a partial response (PR) and 8 a stable disease (SD). Among PR patients, 3 were in the OC group, according to IGCG CA125 criteria. Regarding patients with SD, 4 occurred in patients with OC and one each in patients with cervix, lung, testis, and breast cancer.

Antiepileptic Drugs other than Valproate

We were unable to find studies on antiepileptic drugs other than VPA, namely oxcarbazepine, lamotrigine, gabapentin, pregabalin. We found only one study on the effect of carbamazepine (CBZ), an antiepileptic drug currently used in the treatment of patients with epilepsy and in patients with Bipolar Disorder, on metothrexate (MTX) resistance of OC cells (Toffoli et al., 2000). The main finding from this study supported the hypothesis that CBZ might alter the intracellular transport of folates and modulate, after chronic exposure, the resistance of OC cells towards MTX due to a defective MTX uptake, considering that MTX and folates had common pathways.

Atypical Neuroleptics in Ovarian Cancer

No studies or anecdotal observations are available on the use of quetiapine, aripiprazole, and paliperidone in patients with OC or on animal and cell lines studies.

Olanzapine is increasingly used for the management of cancer patients with chemotherapy-induced nausea and vomiting (off-label indication). A recent study tested the effects of olanzapine treatment on the survivin expression and cell viability of human cancer cell lines, including OC cells. Olanzapine has been found to sensitize them to chemotherapeutic agents such as 5-fluorouracil, gemcitabine, and cisplatin in a survivin expression-dependent manner (Sanomachi et al., 2017).

Olanzapine resulted ineffective in a case report on a chemotherapy-induced acute psychosis, in a 25-years old patient with an ovarian germ cell tumor (Puangthong & Pongpirul, 2015). The patient showed acute behavioral changes after receiving an intensive dose of neo-adjuvant chemotherapy with bleomycin, etoposide and cisplatin, for an OC relapse. She had mood fluctuations, insomnia, and irritability, flights of ideas and hyperactivity, paranoid ideations, auditory hallucinations. The incremental dosage of olanzapine from 5 to 20mg/day failed to control her symptoms during the first week; she was therefore switched to risperidone, at 4 mg/day, with a good clinical response.

Clozapine is an atypical neuroleptic usually administered in treatment-resistant schizophrenic disorders. Its use has been proposed also for treatment-resistant bipolar disorders with psychotic symptoms (off-label indication) (Li, Tang, Wang, & de Leon, 2015). A main concern with the use of clozapine is its effect on blood counts that make difficult its use together with myelosuppressive chemotherapy. The mechanism of clozapine-induced agranulocytosis remains controversial. The pathophysiological mechanisms may involve genetic susceptibility or immune-mediated toxicity. A possible activation of common apoptotic pathways by clozapine, similar to anticancer drugs, has also been hypothesized, but no concrete evidence points to such a synergistic effect. Clozapine-induced leukopenia usually occurs within the 1st year of initiation, and it is non-dose dependent and idiosyncratic (Li, Tang, Wang, & de Leon, 2015).

A case report has been described on a clozapine-stabilized, treatment-resistant bipolar disorder patient with OC requiring chemotherapy (Pakhre, Krishnan, Pattanayak, & Khandelwal, 2016). The patient had a bipolar clinical course characterized by multiple failures to respond to several psychotropic medications, until she started clozapine (200-300 mg/day) in add-on to lithium (900 mg/day), and to lamotrigine, a mood stabilizer commonly utilized to prevent the recurrence of depressive episodes. On these medications, bipolar disorder was stabilized. However, after the diagnosis of an OC (papillary adenocarcinoma Stage IIIC) the patient underwent surgery and chemotherapy with carboplatin. Clozapine was discontinued because of the high likelihood of developing cytopenia. Around 2 weeks after the cessation of clozapine, the patient started to have manic symptoms with irritable mood, increase in goal-directed activity, reduced sleep, and aggressive behaviors. Haloperidol was then added and increased to 20 mg/day with only a mild improvement in manic symptoms. Giving that, clozapine was gradually inserted again (12.5-25 mg for every 3-4 days), reaching a final dose of 275 mg/day, with a significant improvement in mood and behavioral symptoms.

In summary, finding on the use of neuroleptics in bipolar patients with OC is only anecdotal, and providing very limited evidence on the possible therapeutic strategies. However, case reports raised relevant clinical points on the comorbidity between bipolar disorder and OC. Firstly, the diagnosis of a life-threatening disease, such as OC, might induce a relapse/recurrence in patients already treated and stabilized for a bipolar disorder. Secondly, chemotherapy raises practical problems on the management of lifelong treatments (such as clozapine) that might have a safety profile difficult to manage in OC patients.

Discussion

No systematic studies on the treatment of Bipolar Disorders in OC patients are available. Limited information is provided by case reports. This is incomprehensible, form a psychiatric point of view, considering that Bipolar Disorder, in its different forms, is affecting 1-4% of general population as a lifelong, chronic, recurrent disorder. Moreover, patients with Bipolar Disorders constitute a risk group for various somatic comorbidities (such as cancer, dementia and coronary heart disorders) not adequately treated (Nielsen, Kugathasan, Straszek, Jensen, & Licht, 2019). Giving that, it is reasonable to hypothesize that BP disorder patients might receive, at some point in their life, also a cancer diagnoses, including OC.

In a recent meta analysis, It has been demonstrated that patients with OC in the UK are almost twice as likely to experience clinically significant depression and more than four times as likely to experience clinically significant anxiety as women without OC (Watts, Prescott, Mason, McLeod, & Lewith, 2015). Again, no bipolar disorders were detected. However, It is well known from psychiatric and epidemiological samples, that a relevant percentage of patients cross-sectionally diagnosed with '*unipolar depression*' (Major Depressive Episodes, MDE) in psychiatric and non psychiatric settings, might actually have an underlying bipolar diathesis or sub-threshold manifestations of bipolarity that complicates clinical course and treatment response, especially when a longitudinal assessment is performed (Cassano et al., 1999; Cassano et al., 2002; Cassano et al., 2009; Cassano et al., 2012; Nielsen, Kugathasan, Straszek, Jensen, & Licht, 2019).

The lack of information in OC patients is twofold: no studies are available on samples of patients who already have a diagnosis of bipolar disorder and that might receive also a comorbid diagnosis of OC; no systematic observations have been conducted on the new onset of manic, hypomanic, mixed episodes, or bipolar depressive episodes amongst patients who have been diagnosed with OC, with a very limited evidence due to anecdotal case reports. As a consequence, it is difficult to have a consistent evaluation on the pathways for new mood episodes, as triggered by a life-threatening diagnosis such as OC (including the fear of imminent treatments, treatment-related side effects, the fear of cancer progression, the actual progression and the cognitive anticipation of scaring scenarios). Finding on treatment options is also lacking, but some *'indirect'* evidence on mood stabilizers could provide useful suggestions.

Lithium is the gold standard treatment for bipolar disorders and it has been also tested in a number of studies on treatment-resistant OC cells. The rationale for using lithium in patients with OC and BPD is reinforced by studies that highlighted the protective effect of LiCl on cancer proliferation through the inhibition of glycogen synthase kinase-3β (GSK-3β). Treatment with lithium chloride has been shown to be effective by in vitro studies in OC cancer types. Conversely, in vivo studies provided inconclusive evidences, or failed to demonstrate a clinical response at therapeutic dosages.

From a psychiatric point of view, lithium is still the first choice for BPD, and the most effective strategy for a good long-term prognosis (Goodwin, & Consensus Group of the British Association for Psychopharmacology, 2009). Furthermore, lithium is the only treatment effective in suicide prevention in the overall spectrum of mood disorders, which have a suicide risk 20-fold higher, compared to the general population (Sarai, Mekala, & Lippmann 2018). This is a relevant issue in a special population of patients with a life-threatening diagnosis such as OC. It could be also of great clinical importance to clarify whether long-term lithium treatment for a diagnosis of BPD is associated with an increased or a diminished risk of cancer, considering that this is still a controversial issue in the literature (Huang, Hsieh, Huang, & Yang, 2016; Ozerdem, Ceylan, & Targıtay).

Finding on mood stabilizers except for lithium (namely antiepileptic drugs) in OC is also limited. Valproate (VPA) is the only drug with concordant studies in purposing VPA as promising to achieve the goal of overcoming cisplatin resistance of OC in the future, and in supporting drug trials with this agent. Evidence on neuroleptics is scarce with two case reports on clozapine, and risperidone.

This coerced interest in comorbidity between BPD and OC is not easily explainable. We could hypothesize that the absence of clinical studies on bipolar spectrum in OC patients might be due to the fact that, in the routine clinical settings, no formal psychiatric assessment for bipolar disorders is reserved to OC patients. The diagnosis of OC, likewise for other forms of cancer, is considered by definition as emotionally distressing, and thus related to the likelihood of having depressive and anxious symptoms, enhancing these psychological aspects and limiting the detection of bipolar signs (with the exception of acute manifestations, such as agitation or psychotic symptoms).

We could also hypothesize that the instruments commonly used in liaison psychiatry settings are limited to the detection of depression and anxiety. For example, the instrument utilized to assess the presence/absence of anxiety and depressive symptoms in a number of oncology settings, including OC, is the HADS, a scale not widely used for diagnostic purposes by psychiatrists, and not assessing bipolar signs and symptoms (Miniati et al., 2018). It is well known that bipolar disorders frequently go unrecognized in psychiatric and non-psychiatric settings (Benvenuti et al., 2008). The under-diagnosis of hypomania and mania may delay the recognition of illness and the start of an appropriate treatment, therefore worsening the prognosis of Bipolar Disorders, especially when severe comorbid physical conditions occur (Cassano et al., 1999). Part of the delay is due to the fact that patients usually do not present for treatment of the milder forms of mania, such as hypomania, which are rarely perceived as a source of distress (Cassano et al., 2002). Unfortunately, the unrecognized bipolarity is a very common source of antidepressant-refractory depression (Sharma, Khan, & Smith, 2005; Inoue et al., 2006) and suicidality during antidepressant drug treatment (Rihmer & Akiskal, 2006). Moreover, when signs and symptoms such as agitation, racing thoughts, behavioral problems, delusions or hallucinations are detected amongst patients with OC there is a relevant problem of the differential diagnosis between BPD and a number of neuro-psychiatric syndromes. The most important example is the anti-NMDAR encephalitis associated with ovarian teratomas. The syndrome includes symptoms mimicking the onset of a manic/mixed episode (psychomotor agitation, auditory hallucinations, emotional lability, confusion, and incoherent speaking) rapidly followed by a severe autonomic dysregulation. Due to the rarity of anti-NMDA-receptor encephalitis, diagnosis may be delayed while more common conditions, such as BPD or infectious encephalitis, are ruled out. The treatment is including resection of the teratoma and adjunctive

immunotherapy; conversely, psychopharmacological options commonly utilized in manic/mixed episodes of bipolar disorder are scarcely reducing symptomatology (Braverman, Marcus, & Garg, 2015).

Study limitation

There is a lack of information on Bipolar Spectrum signs and symptoms in patients with OC and on the clinical usefulness of their most utilized psychopharmacological treatments. The cross-sectional assessment of patients with OC is a limit to the identification of Bipolar Spectrum Disorders that might have an onset with a depressive episode and then run completely overlooked in the long-term, with the exception of the more severe forms, characterized by agitation or psychotic symptoms. Studies on unipolar depression in OC patients demonstrated that they experience a marked reduction in clinical consultations after the completion of their treatment as they move into the survivorship phase, thus limiting the possibility of longitudinal follow-ups and repeated observations.

Clinical Implications

Available data from literature do not allow a treatment algorithm for patients with OC and bipolar disorders. The use of atypical neuroleptics appears problematic, due to their side effects especially on bloodlines. Conversely, the 'classic' mood stabilizers, such as lithium and valproate, have better tolerability profiles than atypical neuroleptics in OC patients. Their use in patients with bipolar disorder and OC should have a role in daily clinical practice, in consideration of their synergistic action with treatments for OC. Data on cell lines and animal models had empowered researchers to believe that strategies for enhancing cancer therapies might be available with these two psychiatric drugs. Unfortunately, studies on OC patients did not confirm this possibility, but from a different point of view, finding should allow clinicians to consider these drugs as a valid option considering their adequate level of tolerability and safety. Having drugs such as lithium and valproate that certainly do not complicate the course of ovarian cancer is a logical choice option for patients with OC and comorbid bipolar disorders.

We believe that the search for more effective forms of pharmacotherapy in patients with a challenging comorbidity between two severe disorders should begin with a closer examination of the factors that make BPD specifically difficult to study in OC patients. In this special population, the under-diagnosis of BPD is the key point limiting the availability of more accurate treatments' algorithms. As a consequence, the clinical challenge of improving both short and long-term treatments of OC/BPD patients is passing throughout the designs of trials with instruments able to detect the wide range of clinical manifestations of bipolarity, and not only of depressive and anxious symptoms. Future studies should offer interventions better matched to the specific features of the bipolar spectrum disorders.

Concluding remarks

Psychiatric disorders in the context of the overall oncology diseases are complex and incompletely understood. Moreover, finding on available treatments is scarce; only recently there is a need for a systematic multi-disciplinary approach. Advances in tumor cells research and in animal models are beginning to elucidate the biological underpinnings for the choice of mood stabilizers in patients with OC. The new findings in this field have the potential to improve diagnostic approach, to optimize treatment selection, and to facilitate the development of new and evidence-based interventions, still largely unexplored.

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CASE REPORT

PAROXYSMAL TONIC SPASM IN A PATIENT WITH THE SUDDEN ZOLPIDEM WITHDRAWAL: A CASE REPORT

Masoud Keighobadi, Narges Karimi

Abstract

Zolpidem is an imidazopyridine derivative and a non-benzodiazepine hypnotic drug. There are several case reports of zolpidem abuse or dependence and zolpidem withdrawal. This study reports a case of paroxysmal tonic spasm (PTS) after abrupt withdrawal of high dose zolpidem. The case was a 21-year- old male patient with complaints of acute involuntary and painful spasms of all extremities after the sudden withdrawal of taking supratherapeutic zolpidem. In his medical records, He had the history of insomnia and psychiatric disorder . The patient's symptoms improved with intravenous injection of 10 mg diazepam slowly and zolpidem was tapered gradually. This case report indicates that zolpidem has a dependency and abusage properties. To the best of our knowledge , this is the first report of zolpidem withdrawal with PTS.

Key words: zolpidem, withdrawal, paroxysmal painful spasm, dependency, case report

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Introduction

Paroxysmal tonic spasms (PTS) has been described as abrupt onset of attacks in the form of tonic status, either unilateral or bilateral. It usually lasts seconds or minutes and is associated with extreme pain of the limbs. This disorder may be stimulated by intentional activities, sensory stimulation, hyperventilation or occur spontaneously (Abaroa et al., 2013). The patients are alert at the time of attacks and most patients have normal conditions between the attacks (Abaroa et al., 2013). This disorder is usually observed in association with structural lesions of central nervous system (CNS), such as the demyelination lesion and lacunar infarcts of pons and basal ganglia or metabolic abnormalities such as hyperglycemia, hypo- or hypercalcemia (Kellett, Young, & Fletcher, 1997; Marsilia, Gallerinia, Bartaluccia, Marottia, & Marconia, 2018). The exact pathophysiology of tonic spasm has not been determined yet. Zolpidem is an imidazopyridine derivative and a non-benzodiazepine hypnotic drug with a high affinity to α1 subunit of gamma amino butyric acid-A (GABAA) receptor which is prescribed in short-term treatment of insomnia. Zolpidem also has mild anxiolytic, myorelaxant and anticonvulsant effects (Chen, Chen, Liao, Tseng, & Lee, 2012; Monti, Spence, Buttoo, & Pandi-Perumal, 2017). There are several case reports of zolpidem abuse or dependency and zolpidem withdrawal. Zolpidem withdrawal symptoms include insomnia, anxiety, tremor, palpitations, and convulsions (Pourshams, & Malakouti, 2014; Wang, Ree, Chu, & Juang, 2011). One study reported the onset of status dystonicus following zolpidem withdrawal (Kojovi & Gregori Kramberger, 2015). However, to the best of our knowledge, this is the first time to investigate a case of PTS associated with zolpidem withdrawal.

Case presentation

A 21-year- old male patient with history of psychiatric disorder and insomnia from 3 years. was referred to our university hospital (Bou-Ali Sina), Sari city, Mazandaran province, Iran with acute onset of involuntary and painful movements of all extremities and neck. This symptom had been initiated one day before the admission. The sudden muscle spasms were precipitated spontaneously. The attack lasted less than two minute and repeated 10 to 15 times a day. Consciousness and awareness was always preserved during the attacks. The patient presented the abnormal movements that were in dystonic form with neck and head turned to the right, shoulder adduction and internal rotation, extension and stretching of upper and lower limbs along with sparing of face and trunk. The involvement of the limbs was bilateral

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and simultaneous. The patient was able to speak at the time of the attacks but was unable to move until the attack had completely stopped. There was a rapid improvement in muscle contraction and no subsequent confusion. The patient had tachycardia, increased respiration, and diaphoresis during the attacks, though he was normal between attacks. The patient's symptoms were present on awakening and did not change during the physical examination and observation. He had no family history and past medical history of neurological disorders and he was not taking any medication other than zolpidem. In terms of psychiatric disorder, the patient had behavioral disorder approximately 3 years ago. He complained from anxiety, aggressive attacks and insomnia. He started taking zolpidem with dosage of 10 mg daily one year ago. After taking zolpidem, the patient's anxiety and restlessness decreased. After two months, he gradually increased his daily zolpidem consumption to 70-80 mg daily. After 6 months, he abruptly stopped taking zolpidem as a result of dizziness and nightmares. Approximately 24 hours after discontinuation of the drug, he showed the signs of abnormal movements.

At the admission time, the patient was agitated and had increased psychomotor activity. The vital signs of patient were temperature (T)=36.8°C axillary, pulse rate (PR)=90, respiratory rate (RR)=20, O2 Sat=98%, and Blood Pressure (BP) 130/70. The neurological examination was normal. To rule out differential diagnosis, several lab tests and imaging were performed. The lab tests such as complete blood count, blood sugar, electrolytes, urea, calcium, phosphor, magnesium, erythrocyte sedimentation rate, thyroid and liver function tests were normal. Brain and cervical magnetic resonance imaging (MRI) with T1- and T2 weighted, FLAIR, post gadolinium-enhanced T1-weighted sequences, and a DWI sequence was normal. An awake 16-channel electroencephalogram (EEG) with the standard "10–20 system" was performed. It was normal in between attacks. The symptoms of patient improved with intravenously injection of 10 mg diazepam slowly and zolpidem was tapered gradually over one week. Therefore, he was discharged on zolpidem 5 mg bid and followed up for 8 months. After 4 weeks, zolpidem was stopped. After 8 months' follow-up, the patient remained asymptomatic and had no tonic attacks.

Discussion

In this report, we described a male patient developing paroxysmal painful tonic spasms after abrupt discontinuing of high-dose zolpidem. The best of our knowledge, this is the first case of association of PTS with zolpidem withdrawal in the literatures. This patient was consuming zolpidem in the supratherapeutic doses consistently for a long time and therefore he became dependent on it. He had withdrawal symptoms with PTS after 24 hours of its discontinuation. He had no past history of neurological disorders and he was not taking any medicine other than zolpidem. Brain and cervical MRIs and also interictal EEG were normal. Zolpidem is a short-effect hypnotic drug that augments GABAergic neurotransmission through the benzodiazepine binding site on specific GABA-A receptors (α1 subunit) but is not deliberated a typical benzodiazepine because of lack of diazepine cycle in chemical structure (Chen, Chen, Liao, Tseng, & Lee, 2012). Zolpidem was approved for the short-term treatment of insomnia almost twenty years ago (Monti, Spence, Buttoo, & Pandi-Perumal, 2017; Chen, Chen, Liao, Tseng, & Lee, 2012). Several reports described abuse and dependency and also withdrawal symptoms with zolpidem (Chen, Chen, Liao, Tseng, & Lee, 2012; Pourshams, & Malakouti, 2014; Wang, Ree, Chu, & Juang, 2011). The withdrawal symptoms of taking high-dose zolpidem are similar to the symptoms of benzodiazepines withdrawal, including tremor, insomnia, anxiety, autonomic nervous system dysfunction, and generalized tonic–clonic seizures (Chen, Chen, Liao, Tseng, & Lee, 2012).

Recently, Rossi et al reported a case with focal bilateral movement seizure due to abrupt stopping of chronic lormetazepam abuse (Rossi, Di Stefano, Lizzos, & Deiana, 2020). Some studies described rare symptoms of zolpidem withdrawal including status dystonicus and catatonia (Kojovi & Gregori Kramberger, 2015, Hsieh, Chen, Chiu, & Chang, 2011). Status dystonicus is life threatening complication of generalized dystonia associated with respiratory and metabolic complications (Kojovi & Gregori Kramberger, 2015). One of the differential diagnoses of paroxysmal movement disorder is functional (psychogenic) movement disorders (FMDs) that the clinical characteristics of this disorder such as variability, instability, suggestibility, distractibility, and suppressibility during physical examination helps to identify it (Thenganatt & Jankovic, 2019). in this case report, we described zolpidem-related withdrawal PTS. The pathophysiology of PTS is unclear. Although spreading activation of damage axons has been described, it is still a controversial issue (Abaroa et al., 2013). However, the exact mechanism of developing PTS following zolpidem-withdrawal is still unclear. Some studies have shown that GABA-A receptors may be present in different parts of the CNS and may be connected to other sites of GABA receptors. Hence, the sudden discontinuation of the drug probably caused a prompt reduction in GABA-A transmission in the CNS (Aragona, 2000). It is hypothesized that GABAergic depletion may play a role in causing PTS. Since the results of imaging, EEG, and lab tests were normal, it was postulated that the cause of tonic spasms in this patient was probably non-epileptic spasm due to abrupt discontinuation of zolpidem. A paroxysmal PTS is usually painful and does not have a clonic phase, whereas an epileptic spasm is usually painless and its duration is shorter than PTS. Accordingly, an ictal EEG and video-EEG are helpful in differentiating these two conditions. The symptoms of this patient improved with the injection of diazepam intravenously similar to the study carried out by Chen (Chen, Chen, Liao, Tseng, & Lee, 2012).

Conclusion

This case report indicated that zolpidem is a drug that has a dependency and abusage properties. To the best of our knowledge, this is the first case study to report a possible association between PTS and withdrawal of zolpidem. Although the awareness of patient was preserved during the attacks and interictal EEG, and imaging were normal, but epileptic spasm cannot be completely ruled out. In this study, we could not perform video-EEG monitoring and ictal EEG due to some limitations.

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