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MOOD DISORDERS (E BACA-GARCIA, SECTION EDITOR)

Possible Pharmacodynamic and Pharmacokinetic Drug-Drug Interactions That Are Likely to Be Clinically Relevant and/or Frequent in Bipolar Disorder

Jose de Leon [1,2,3] · Edoardo Spina [4]

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Abstract

Purpose of Review Patients with bipolar disorder are frequently treated with polypharmacy. This article should provide clinicians with an understanding of how polypharmacy can contribute to pharmacokinetic and pharmacodynamic drug-drug interactions (DDIs).

Recent Findings The pharmacokinetics and pharmacodynamics of lithium and other mood stabilizers (valproate, lamotrigine, carbamazepine, oxcarbazepine, and eslicarbazepine), antipsychotics, and selective serotonin reuptake inhibitors (SSRIs) were reviewed and summarized in the first four tables describing their pharmacokinetic and pharmacodynamic mechanisms.

Summary Four tables summarized the DDIs which are likely to be clinically relevant in adults with bipolar disorder: two for mania treatments (with and without carbamazepine), one for maintenance treatments, and one for depression treatments. The purpose is to be practical, helping clinicians pay attention to and manage polypharmacy, avoiding adverse drug reactions (ADRs) in patients with bipolar disorder, including both the frequent ADRs and those rare but potentially lethal ADRs. Future articles should improve these tables.

Keywords Anticonvulsant · Antidepressant · Antipsychotic · Bipolar disorder · Drug interactions · Lithium

Introduction

Polypharmacy (or polytherapy) appears to be the norm around the world in patients with bipolar disorder [1••]. In a large pragmatic US multicenter randomized clinical trial (RCT), complex polypharmacy involving at least four medications was utilized in one in five individuals with bipolar disorder [2]. During the 2010s, the pharmacological guidelines for bipolar disorder provided different pharmacological recommendations for manic, depressive, and maintenance phases [3–10]. They usually recommended monotherapy as a first step but then moved to combinations of drugs in subsequent steps.

As psychiatric textbooks do not usually pay attention to drug-drug interactions (DDIs) [11], bipolar disorder guidelines also pay little attention to them. A search for the term "drug interaction" provided no results for four guidelines [4–6, 10]. The Florida guideline used the term once as a footnote for a table [9].

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✉ Jose de Leon
jdeleon@uky.edu

[1] University of Kentucky Mental Health Research Center at Eastern State Hospital, 1350 Bull Lea Road, Lexington, KY 40511, USA

[2] Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain

[3] Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain

[4] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Two results [7] were found in one guideline, and three in another [8], but no examples were included. The British guideline for pharmacologists used the term several times with some specific examples in their appendix [3].

Literature Search for DDIs in Order to Provide Recommendations for Clinicians

Since 2006, the two authors have collaborated in searching the literature, looking for DDIs of psychiatric drugs so seven DDI review articles [12–14, 15•, 16, 17•, 18••] could be written. An October 2017 PubMed search (with no time limit, focused on adults and including animal studies) provided new articles beyond those hundreds of articles previously reviewed. The reference list of any new article was reviewed for any previously unidentified article.

Clinical Classification of DDIs

As in prior articles [15•, 16, 17•], we used a clinical classification of DDIs based on changes in safety, which pharmacologists call adverse drug reactions (ADRs), or in efficacy. This classification categorizes DDIs as having (1) beneficial (positive) effects (increased efficacy and/or safety) or (2) harmful (negative) effects (decreased efficacy and/or safety).

Pharmacological Classification of DDIs

Pharmacological mechanisms divide DDIs into pharmacokinetic and pharmacodynamic DDIs. A pharmacokinetic DDI is associated with a modification in the serum concentration of either the drug or its metabolite(s) and can be studied in vivo by therapeutic drug monitoring (TDM) [19]. Although psychiatric textbooks tend to ignore pharmacokinetic DDIs [11], they are extensively addressed by pharmacological journals. Pharmacodynamic DDIs are not easy to study since they do not cause TDM changes and for in vivo study, future advances in brain imaging will be required. In our experience, clinically relevant pharmacodynamic DDIs are frequent in the clinical environment, although very few articles describing them are published [11].

Pharmacokinetic DDIs They reflect changes in absorption, distribution, metabolism, or excretion of a drug and/or its metabolite(s). Although on rare occasions protein binding can be associated with clinically relevant DDIs for valproate [20], most of the pharmacokinetic DDIs with potential for clinical relevancy in bipolar disorder occur during drug metabolism with inducers or inhibitors. Inducers are drugs that, acting at the nuclear receptors, increase the synthesis of the metabolic enzyme [21, 22]. They usually require several weeks to produce maximum effects and disappear after withdrawal [21]. Adding an inducer is associated with a decrease in the serum concentration of the induced drug, while discontinuation is associated with increases. Inhibitors bind to the metabolic enzyme and make it inactive. Adding an inhibitor is associated with an increase in the serum concentration of the inhibited drug, while discontinuation is associated with decreases. The half-life of the inhibitor is what determines the amount of time needed for maximum inhibition. Some of the selective serotonin reuptake inhibitors (SSRIs), such as paroxetine or fluoxetine, are called non-competitive inhibitors by pharmacologists since they bind irreversibly to the enzyme and cannot be displaced by the inhibited drug. Besides the typical inhibitors, any drug in a situation of compromise, frequently when multiple drugs saturate a metabolic pathway, can behave as an inhibitor and inhibit its own metabolism; this is called competitive inhibition and is easily reversible by decreasing the substrate dosage.

Pharmacodynamic DDIs They take place directly at the site of action of a drug or indirectly by interfering with another physiological mechanism. Pharmacologists classify them as (1) additive (i.e., equal to the sum of the effects of the individual drugs), (2) synergistic (i.e., the combined effects are greater than expected from the sum of individual effects), or (3) antagonistic (i.e., the combined effects are less than additive). There is no data for determining whether the pharmacodynamic DDIs seen in bipolar patients are additive or synergistic.

Problems with this Pharmacological Classification This pharmacological classification has two simplifications [18••]: (1) inducers can induce endogenous compounds and these can lead to DDIs that are probably better classified as pharmacodynamic and (2) DDIs can be used by clinicians to counteract ADRs.

In the pharmacological sense, the induction of endogenous compounds is a pharmacokinetic effect [21], but to a clinician, these DDIs may resemble other physiological actions of AEDs. An increased risk of osteoporosis in bipolar patients may be an example of this type of unusual DDI. The literature supports the possibility that long-term use of those antipsychotics with high potential for causing hyperprolactinemia may increase the risk of osteoporosis. This is a pharmacodynamic effect, and another pharmacodynamic effect, probably at the bone serotonergic mechanism, explains why SSRIs may also increase the risk of osteoporosis. Although no study has explored the long-term risk of combining hyperprolactinemia-inducing antipsychotics and SSRIs, it is reasonable to expect pharmacodynamic, additive, or synergistic effects contributing to the risk of osteoporosis. Carbamazepine is a potent inducer and, as with other inducers, has been firmly associated with osteoporosis which is explained by a potent induction of vitamin D metabolism [21]. Thus, when long-term carbamazepine treatment is associated with long-term SSRI use, pharmacological mechanisms suggest that a DDI is possible; this is a combination of the pharmacokinetic effect of carbamazepine on the endogenous metabolism of vitamin D and a pharmacodynamic effect of the SSRI. To simplify, we tend to call this a pharmacodynamic DDI [15•]. Simplification is important when talking about osteoporosis risk in bipolar patients, since some clinical studies [23] and some animal studies [24] indicate that lithium may protect from osteoporosis; thus, combining lithium with SSRIs has the potential of causing an antagonistic DDI and may reduce the risk of osteoporosis from SSRIs.

Using an ADR to counteract the ADR of another drug may be better described as a management strategy or clinical strategy for reducing ADRs rather than a pharmacodynamic DDI per se, but it is simpler to classify it as a beneficial pharmacodynamic DDI [18••]. An example of such a clinical strategy is to use topiramate for decreasing weight gain secondary to other drugs, including antipsychotics.

Summary of the Pharmacokinetics and Pharmacodynamics of the Main Drugs Used in Bipolar Disorder

Table 1 provides a brief summary of the pharmacokinetics and pharmacodynamics of lithium, the mood stabilizer *par excellence*. Lithium is not metabolized but renally excreted [25] and has complex pharmacodynamic actions [26•]. Table 2 focuses on antiepileptic drugs (AEDs) with mood stabilizer properties. Valproate is a drug with complex metabolism that appears to vary with the dose [27]. Traditionally, it has been considered an inhibitor, but it may also be a mild inducer [21]. It is probably both a mild inducer and a competitive inhibitor for olanzapine and clozapine [21]. Valproate is

Table 1 Pharmacokinetics and pharmacodynamics of lithium for adult patients with bipolar disorder

LITHIUM

PHARMACODYNAMICS

Efficacy

Mania: *unclear (one theory*: ↓ *protein kinase C activity)*
Mood stabilizer: *unclear (one theory*: *by suppressing inositol signaling)*
Antidepressant augmentation: *unknown*
Antisuicidal effects: *unknown*
Possible neuroprotective effects: *unknown*
Leukocytosis: *complex*

Safety

Tremor: *(dose-related) unknown*
Cognitive impairment: *(possibly dose-related) unknown*
Extrapyramidal symptoms by itself or ↑ AP-induced: ↓ *dopaminergic activity in basal ganglia*
Rare but concerning neurological ADRs: pseudotumor cerebri, residual after intoxication, confusional states
Weight gain: *(possibly dose-related) unknown*
Hyperlipidemia according to case reports: *unknown*
Serotonin syndrome during polypharmacy: ↑ *serotonin activity at brain and periphery*
Nausea, vomiting or diarrhea: *unknown (can happen at onset but later on are dose-related)*
Polyuria: *blocking ADH at kidney*
Kidney damage: *unclear (one theory*: *by antiapoptotic effect)*
Rare but concerning renal ADRs: acute nephrotic syndrome and possible ↑ renal cancer
Edema: *unknown*
Hypothyroidism: *interferes with release and synthesis of thyroid hormones*
↑ Serum calcium levels: *interfere with parathyroid hormone mechanisms*
Possible ↑ osteogenesis: *not well understood*
Cardiac arrhythmias (sinus node dysfunction/atrioventricular blockade): *antagonism of sodium channels*
Potential to exacerbate acne: *not well understood*
Potential to exacerbate psoriasis: *not well understood* (*one theory*: *by suppressing inositol signaling)*
Alopecia: *not well understood*

PHARMACOKINETICS

Renal elimination (depends on glomerular filtration rate, sodium retaining and eliminating mechanisms)

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

ADR adverse drug reaction, *AP* antipsychotic, *C* concentration

Table 2 Pharmacokinetics and pharmacodynamics of AEDs as mood stabilizers for adult patients with bipolar disorder

PHARMACODYNAMICS

Efficacy

AE (CBM, VPA, LTG): different mechanisms[a]
Mania (CBM, VPA): *unclear (one theory: ↓ protein kinase C activity)*
Mood stabilizer (VPA, CBM): *unclear (one theory: suppressing inositol signaling)*
↓ Risk of depressive relapse (LTG): *unknown (one theory: down-regulation of arachidonic acid cascade[b])*
↓ Some types of pains (CBM): ↓ *activity of voltage-dependent sodium or calcium channels*
Migraine prophylaxis (VPA): *unknown*

Safety

Sedation: *(dose-related) same as mechanism for AE*
Cognitive impairment: *(possibly dose-related) same as mechanism for AE*
Balance and motor-ocular disturbances: *(possibly dose-related) same as mechanism for AE*
Weight gain (CBM, VPA): *unknown*
Nausea and vomiting: *possibly same as mechanism for AE*
Hyponatremia (CBM[c]): *SIADH and/or increased sensitivity to ADH*
↑ liver enzymes: *unknown*
Alopecia (VPA and possible CBM): *not well understood*
Thrombocytopenia (VPA): *(dose-related) unknown toxic mechanism*
Leukopenia (CBM, VPA): *unknown*
PR interval prolongation (CBM > LTG): ↓ *activity of cardiac voltage-dependent sodium channels*
SJS/TEN (CBM, LTG > others[d]): *immunological mechanisms*
Other rare ADRs for VPA: interference with coagulation, hyperammonemic encephalopathy, pancreatitis
Rare ADRs but potentially lethal (CBM,[e] VPA): agranulocytosis/aplastic anemia, liver injury

INDUCTION OF ENDOGENOUS COMPOUNDS

Osteoporosis (CBM > other[f]): *induction of vitamin D metabolism*
Thyroid disturbances (CBM): *induction of thyroid hormone metabolism*
Hyperlipidemia (CBM > other[g]): *induction of enzymes involved in lipid metabolism*
Sexual disturbances (CBM > other[h]): *induction of enzymes involved in sexual hormone metabolism*

PHARMACOKINETICS

VPA
Therapeutic doses:[i] **UGT > ß-oxidation > CYP** (Inhibitor[j]
Possible inducer[k]
Free VPA is the active compound[l])

Complex DDI with CBM	Do not combine[m]
Complex DDI with OXC or ESL	Do not combine or be careful and use TDM
Inhibitor of LTG	LTG dose: 0.5×. Be careful with SJS/TEN
Mild inducer or inhibitor of OLA	May be relevant in some patients. Use TDM
Mild inducer of ARI	ARI dose: 1.25× or use TDM
Inhibitor of PAL	PAL dose: 0.50. Use TDM
Possible inhibitor of ASE	Not well studied. Consider TDM
Inhibited by FLUO, FLUV	Do not combine: ↑ VPA levels described
Geriatric, aspirin/NSAID, renal/liver impairment[l]	Be very careful. Measure free VPA

Table 2 (continued)

LTG	Induced by CBM	LTG dose: 1.5×. SJS/TEN after CBM D/C
UGT1A4[n] (Mild inducer[o] and self-inducer)	≥ 1200 mg/day OXC (or ESL)	Use LTG TDM. SJS/TEN after OXC D/C
	Inhibited by VPA	LTG dose: 0.5×. Be careful with SJS/TEN
	AP	Mild and no clinically relevant DDIs[p]
	SSRIs	Mild and no clinically relevant DDIs[q]
CBM	Complex DDI with VPA	Do not combine[m]
CYP3A4 is main metabolic pathway during induction (Potent CYP and UGT inducer including self-induction[r])	Inducer of LTG	LTG dose: 1.5×. SJS/TEN after CBM D/C
	Inducer of OXC or ESL	Be very careful when switching from CBM
	Extreme inducer: LUR, CAR, QUE, SER	Do not combine.
	Very potent inducer: PAL, OLA	PAL dose: 3× (OLA dose 2–3×). Use TDM
	Potent inducer: ARI, HAL, RIS	AP dose: 2×. Use TDM
	Inducer: ASE	Not well studied. Consider TDM
	Mild inducer: ZIP, CIT, ESCIT	No need for dose change. Consider TDM
	Not relevant inducer: PAR, FLUO, FLUV	No need for dose change. Consider TDM
	Inducer of medical meds and benzodiazepines	Be aware[s]
OXC[t] pro-drug[u] (Mild inducer of CYP3A4 and UGTS	Not a self-inducer	Different from CBM
Moderate inhibitor of CYP2C19)	Complex DDI with VPA	Do not combine or be careful and use TDM
	≥ 1200 mg/day OXC and LTG	Use LTG TDM. SJS/TEN after OXC D/C
	CBM is inducer of OXC	Be very careful when switching from CBM
	≥ 1200 mg/day OXC and AP or SSRIs[v]	See CBM DDIs and consider TDM
	≥ 1200 mg/day OXC and other meds[v]	See CBM DDIs
ESL[t] pro-drug[w] (Mild inducer of CYP3A4 and UGTS	Not a self-inducer	Different from CBM
Moderate inhibitor of CYP2C9 and CYP2C19)	Complex DDI with VPA	Do not combine or be careful and use TDM
	≥ 1200 mg/day ESL and LTG	Use LTG TDM. SJS/TEN after ESL D/C
	CBM is inducer of ESL	Be very careful when switching from CBM
	≥ 1200 mg/day ESL and AP or SSRIs[v]	See CBM DDIs and consider TDM
	≥ 1200 mg/day ESL and other meds[v]	See CBM DDIs

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

ADH antidiuretic hormone, *ADR* adverse drug reaction, *AE* antiepileptic, *AED* antiepileptic drug, *AP* antipsychotic, *ARI* aripiprazole, *ASE* asenapine, *CAR* cariprazine, *CBM* carbamazepine, *CIT* citalopram, *CYP* cytochrome, *D/C* discontinuation, *DDI* drug-drug interaction, *ESCIT* escitalopram, *ESL* eslicarbazepine, *FLUO* fluoxetine, *FLUV* fluvoxamine, *GABA* gamma-aminobutyric acid, *HAL* haloperidol, *LTG* lamotrigine, *LUR* lurasidone, *MHD* monohydroxy derivative, *NSAID* non-steroidal antiinflammatory drug, *OLA* olanzapine, *OXC* oxcarbazepine, *PAL* paliperidone, *PAR* paroxetine, *QUE* quetiapine, *RIS* risperidone, *SER* sertraline, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis, *SSRI* selective serotonin reuptake inhibitor, *TDM* therapeutic drug monitoring, *UGT* uridine 5′-diphospho-glucuronosyltransferase, *VPA* valproate, *ZIP* ziprasidone

[a] CBM: ↓ activity of voltage-dependent sodium channels; LTG: ↓ activity of voltage-dependent sodium and calcium channels; VPA: complex including ↑ GABAergic neurotransmission

[b] This theory defends all mood stabilizers would act in that way

[c] This may be the only ADR that is more frequent in OXC and ESL than in CBM. VPA very rarely has been associated with SIADH

[d] ESL, OXC, and VPA have been associated with SJS/TEN only very rarely

[e] Unlike CBM, OXC and ESL do not appear to cause these potentially lethal ADRs

[f] OXC and VPA have been associated with osteoporosis and appear to be mild inducers of vitamin D. ESL is likely to cause osteoporosis. LTG has not been definitively associated with osteoporosis

[g] Although it has not been well-studied, OXC and ESC may have mild inductive effects in some CYP enzymes. VPA can ↓ high density lipoprotein cholesterol but the mechanism is not known

[h] OXC and ESC appear to be mild inducers of sexual hormones. In fertile women with epilepsy, VPA has been associated with polycystic changes in the ovaries, high serum testosterone concentrations (hyperandrogenism) and menstrual disorders. It is not established whether these changes occur in non-epileptic women taking VPA for years

[i] VPA metabolism changes with dosing. At therapeutic doses, the enzymes in order of importance are UGT > ß-oxidation > CYP. At low doses, the enzymes in order of importance are ß-oxidation > UGT > CYP. Multiple UGTs are involved including hepatic UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7, along with the primarily intestinal UGT1A8 and UGT1A10. Several CYPs are involved, including CYP2C9, CYP2C19, and CYP2A6

[j] Clinically relevant inhibitor of CYP2C9, several UGTs, and epoxide hydroxylase

[k] Inducer activity has not been well investigated. It appears to be a self-inducer [26•] and inducer of some APs, but enzymes are not well identified

[l] Free VPA is approximately 10% of the total VPA, but the percentage increases as total VPA concentration increases and serum proteins get saturated. Situations such as geriatric age, co-prescription of aspirin or NSAIDs, and renal or liver impairment are associated with ↑ free VPA due to ↓ serum proteins and/or displacement by other compounds [20]

[m] VPA and CBM have complex pharmacodynamics DDIs and pharmacokinetic DDIs. VPA may inhibit CBM metabolism while CBM tends to induce VPA metabolism. A displacement of protein binding with ↑ serum free VPA is also possible [22]. It is better not to combine VPA and CBM unless the clinician has great expertise on DDIs and is willing to measure serum free VPA

[n] There are contradictory results concerning whether UGT27B may or may not also be important for LTG metabolism [21]

[o] It is a mild UGT inducer; this is why it can cause initial mild (< 20% serum concentration decrease within 2 weeks) induction of its own metabolism in patients who are not taking more potent UGT inducers [21]

[p] Some articles have described clinically relevant decreases of serum QUE or OLA concentrations by LTG [17•]

[q] Some articles have described clinically relevant increases of serum LTG concentrations by some SSRIs [17•]

[r] CBM is (1) an extremely potent inducer of CYP2B6 and CYP3A4, (2) a moderate inducer of CYP1A2 and CYP2A6, and (3) a mild inducer of CYP2C9 and CYP2C19. CYP2D6 cannot be induced. CBM is a UGT inducer but the effect in specific isoenzymes has not been well studied [22]. Due to self-induction, CBM does not reach steady state until 3–5 weeks after the last dose increase [21]

[s] CBM should not be combined with oral contraceptives. Most statins and calcium channel blockers are dependent on CYP3A4 for their metabolism and should not be combined with CBM. A prior article describes compound exceptions for these drug classes and DDIs with benzodiazepines [21]. CBM is also a *p*-glycoprotein inducer and this can decrease the effects of other drugs [22]

[t] OXC and ESL are not approved for bipolar disorder. We include them in the pharmacokinetic bottom part of the table because in our experience some clinicians prefer to use them instead of CBM to avoid ADRs and DDIs

[u] OXC is rapidly reduced by a cytosol arylketone reductase to the MHD, also called licarbazepine, which is the clinically relevant metabolite. OXC acetate is a pro-drug of both enantiomers S-MHD (80%) and R-MHD (20%). MHD is cleared by glucuronidation and, less so, by oxidation to an inactive metabolite. Renal excretion is the major route for oxcarbazepine excretion (80% of dose) [21]

[v] OXC and ESL should not be co-prescribed with oral contraceptives. The effects of high doses of OXC or ESL have not been well studied for other CYP3A4 drugs. We recommend that if clinicians are using high doses of them, they should consider them potentially similar to CBM. We consider ≥ 1200 mg/day a high dose of OXC with clinically-relevant risk for induction. The literature does not provide enough information to determine which dose of ESL has high potential to act as a relevant inducer in an average patient but in some studies ≥ 1200 mg/day appear to have inductive effects

[w] ESL acetate is rapidly and extensively (95%) hydrolyzed in the first-pass metabolism at the liver and gut to eslicarbazepine (also known as S-licarbazepine or S-MHD). Another 5% is oxidized to oxcarbazepine and R-licarbazepine (or R-MHD). Metabolites eliminated in the urine include two thirds of the total dose as S-MHD and one third as glucuronide conjugates probably mediated by UGT1A1 [21]

Table 3 Pharmacokinetics and pharmacodynamics of antipsychotic use for adult patients with bipolar disorder

PHARMACODYNAMICS

Efficacy

Mania and mood stabilizer (probably common to all): *D_2 antagonism at basal ganglia and cortex*

Antidepressant in bipolar disorder (LUR, QUE): *unknown*

Safety

Extrapyramidal symptoms (HAL > PAL, RIS, LUR > other > QUE): *D_2 antagonism at basal ganglia*

Hyperprolactinemia (HAL, PAL, RIS > other > QUE > ARI): *D_2 antagonism at tubero-infundibular system*

Weight gain (OLA > other > ARI, HAL, LUR, ZIP): *H_1 and 5-HT_{2C} antagonism at brain*

Sedation (ASE, OLA > QUE > other): *H_1 antagonism at brain*

Activation and early insomnia (ARI, ZIP): *not well understood*

↓ seizure threshold (OLA, QUE > other): *not well understood*

Hyperglycemia/hyperlipidemia: *secondary to weight gain*

Hyperglycemia/hyperlipidemia (OLA, QUE): *direct effects on metabolism*

Sexual ADRs (HAL, RIS, OLA > other): *hyperprolactinemia and α, H and M antagonism at periphery*

Orthostatic hypotension (RIS, QUE): *α_1 antagonism at periphery*

Anticholinergic ADRs including constipation and urinary retention(OLA > high dose QUE): *M antagonism at periphery*

Nausea (ARI, LUR, ZIP): *unknown*

Swallowing impairment (probably all but not well studied): *unknown*

↑ QTc and risk for Torsades de pointes (RIS, ZIP > other): *antagonism of repolarizing K channels at heart*

Rare but concerning ADRs: neutropenia, VTE, heat stroke, hyponatremia, ↑ liver enzyme, NMS

PHARMACOKINETICS

CYP1A2/UGT[a]	CBM (potent inducer)	Dose: 2–3×. Use TDM
OLA	≥ 1200 mg/day OXC (mild inducer)	Not studied: mild ↑ dose or use TDM
	VPA (mild inducer and/or inhibitor)	May be relevant in some patients. Use TDM
	Other SSRIs not listed on the line below	No relevant DDI
	FLUV (potent CYP1A2 inhibitor)	Dose: 0.3–0.5× or use TDM
CYP3A4	CBM (potent CYP3A4 inducer)	Do not use
CAR	≥ 1200 mg/day OXC (mild CYP3A4 inducer)	Do not use unless TDM is accessible
LUR	Other SSRIs not listed on the line below	No relevant DDI
QUE	FLUO, FLUV (mild/mod. CYP3A4 inhibitor)	Monitor for ADRs
CYP2D6/CYP3A4[b]	CBM (potent CYP3A4 inducer)	Dose: 2×. Use TDM
ARI	≥ 1200 mg/day OXC (mild CYP3A4 inducer)	Not studied: mild ↑ dose or use TDM
RIS (HAL[3])	Other SSRIs not listed on the lines below	No relevant DDI
	FLUV, high[d] SER (mild CYP2D6 inhibitor)	Monitor for ADRs; use TDM
	PAR (potent CYP2D6 inhibitor)	Dose: 0.5× or use TDM
	FLUO (inhibitor: CYP3A4/potent CYP2D6) CYP2D6 PM and CYP3A4 inhibitor	Dose: 0.25× or use TDM

Table 3 (continued)

ARI	VPA (mild inducer)	Dose: 1.25× or use TDM
HAL	HAL is a CYP2D6 inhibitor: FLUO, PAR	Use other SSRIs
Aldehyde oxidase (and CYP3A4): ZIP	Potent induction of CYP3A4: CBM	No need for dose change. Consider TDM
	Mild/mod. CYP3A4 inhibitors: FLUO, FLUV	No need for dose change. Consider TDM
UGT1A4 and CYP1A2: ASE	Inducer: CBM	Not well studied. Consider TDM
	≥ 1200 mg/day OXC (mild UGT inducer)	Not well studied. Consider TDM
	Possible inhibitor: VPA	Not well studied. Consider TDM
	Other SSRIs not listed on the lines below	No relevant DDI
	FLUV (potent CYP1A2 inhibitor)	Dose: 0.50–0.75×. Use TDM
	ASE is CYP2D6 inhibitor: FLUO, PAR	Use other SSRIs
Renal but CYP3A4 relevant under induction: PAL	Potent CYP3A4 induction: CBM	Dose: 3×. Use TDM
	Mild CYP3A induction (≥ 1200 mg/day OXC)	Not well studied. Use TDM
	VPA (mild inhibitor)	Dose: 0.50. Use TDM
	SSRIs	No need for dose change. If ADR use TDM

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

α alpha, *ADR* adverse drug reaction, *ARI* aripiprazole, *ASE* asenapine, *CAR* cariprazine, *CBM* carbamazepine, *CYP* cytochrome, *DDI* drug-drug interaction, *FLUO* fluoxetine, *FLUV* fluvoxamine, *H* histamine, *HAL* haloperidol, *K* potassium, *LUR* lurasidone, *M* muscarinic, *NMS* neuroleptic malignant syndrome, *OLA* olanzapine, *OXC* oxcarbazepine, *PAL* paliperidone, *PAR* paroxetine, *PM* poor metabolizer, *QUE* quetiapine, *QTc* QT corrected interval, *RIS* risperidone, *SSRI* selective serotonin reuptake inhibitor, *TDM* therapeutic drug monitoring, *UGT* uridine 5′-diphospho-glucuronosyltransferase, *VPA* valproate, *VTE* venous thromboembolism, *ZIP* ziprasidone

[a] Clozapine is similar to olanzapine. See prior review article [17•]

[b] Brexpiprazole and iloperidone have similar DDIs due to their mixed metabolic profile CYP2D6/CYP3A4 [17•]

[c] HAL appears to be metabolized by CYP2D6 and UGT. Data on HAL DDIs is limited. Currently, we recommend the dose corrections factor used for CYP2D6/CYP3A4 drugs or even better TDM. Carbamazepine and smoking are inducers of haloperidol metabolism. CYP2D6 PMs appear to be more prone to HAL ADRs

[d] Sertraline appears to be a clinically relevant CYP2D6 inhibitor only in high doses

Table 4 *Pharmacokinetics and pharmacodynamics* of SSRI use for adult patients with bipolar disorder

PHARMACODYNAMICS

Efficacy

Antidepressant (and antianxiety): *selective inhibition of serotonin transporter*[a]

Safety

Akathisia (rarely of other EPS): ↓ *dopaminergic activity at basal ganglia*
Rarely hyperprolactinemia: ↓ *dopaminergic activity at tubero-infundibular system*
Weight gain (PAR): H_1 *antagonism at brain*
Insomnia: *not well understood*
Nausea/vomiting: *probably inhibition of serotonin transporter*
Diarrhea (SER): *unknown*
Sexual ADRs: *probably serotonergic mechanisms*
Anticholinergic ADRs including constipation and urinary retention (PAR): *M antagonism at periphery*
Discontinuation syndrome (PAR > other > FLUOX): *probably serotonergic mechanisms*
Risk for bleeding: *serotonin depletion in platelets due to inhibition of transporter and other mechanisms*
Risk for osteoporosis: *probably serotonergic mechanisms in bones*
Serotonin syndrome during polypharmacy: ↑ *serotonin activity at brain and periphery*
↑ QTc and risk for Torsades de pointes: *antagonism of repolarizing K channels at heart*
Hyponatremia (usually in geriatric patients): *SIADH and/or increase in ADH sensitivity*
Very rare but concerning ADR: liver injury

PHARMACOKINETICS

PAR		
CYP2D6 (Inhibitor of CYP2D6: potent)	CBM	No relevant DDI
	VPA	No relevant DDI
	ARI, RIS[b]	AP dose: 0.5× or use TDM
	ASE and HAL are CYP2D6 inhibitors	Do not combine
FLUO (Inhibitor of CYP2D6: potent; CYP2C9: moderate; CYP2C9/CYP3A4:weak to moderate)	CBM	No relevant DDI
	VPA	Do not combine: ↑ VPA levels described
	ARI, RIS[b]	AP dose: 0.25× or use TDM
	ASE and HAL are CYP2D6 inhibitors	Do not combine
SER		
CYP2B6 (In high doses: a weak to moderate CYP2D6 inhibitor)	CBM (potent CYP2B6 inducer)	Avoid. SER dose: 3× or better TDM
	≥ 1200 mg/day OXC	Not studied: mild ↑ SER dose or use TDM
	VPA	No relevant DDI
	ARI, RIS[b]	Monitor for AP ADRs. Use AP TDM if high doses of SER
CIT, ESCIT		
CYP2C19	CBM	Usually not relevant (CIT dose only 1.33×)
(Inhibition is not clinically relevant)	VPA	No relevant DDI
	Antipsychotics	No relevant DDI in most cases

Table 4 (continued)

FLUV[c]	CBM	No relevant DDI
CYP1A2/CYP2D6 (Inhibitor of: CYP1A2/CYP2C19: potent		
CYP2C9/CYP3A4: moderate	VPA	Do not combine: ↑ VPA levels described
CYP2D6: weak)	OLA	OLA dose: 0.3–0.5× or use TDM
	ARI, RIS[b]	Monitor for AP ADRs. Use AP TDM if you combine

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

ADH antidiuretic hormone, *ADR* adverse drug reaction, *AP* antipsychotic, *ARI* aripiprazole, *ASE* asenapine, *CBM* carbamazepine, *CIT* citalopram, *CYP* cytochrome, *ESCIT* escitalopram, *DDI* drug-drug interaction, *EPS* extra-pyramidal symptoms, *FLUO* fluoxetine, *FLUV* fluvoxamine, *K* potassium, *M* muscarinic, *PAR* paroxetine, *OLA* olanzapine, *QTc* QT corrected interval, *RIS* risperidone, *SER* sertraline, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *SSRI* selective serotonin reuptake inhibitor, *TDM* therapeutic drug monitoring, *VPA* valproate

[a] This is not a definitively proven theory due to a mismatch in chronology: reuptake inhibition starts within hours but antidepressant response takes a few weeks

[b] Brexpiprazole and iloperidone have similar DDIs due to their mixed metabolic profile: CYP2D6/CYP3A4

[c] FLUV is not approved for depression in the USA. Table 8 does not include FLUV

susceptible to clinically relevant DDIs at the protein-binding level [20].

Lamotrigine is a mild inducer. Carbamazepine is a potent inducer [21] and induces the metabolism of most of the psychiatric drugs. Table 2 includes at the bottom two carbamazepine analogs, oxcarbazepine, and the acetate of eslicarbazepine. They are not approved for bipolar disorder but are used by clinicians due to their similarity to carbamazepine, although with less potential for ADRs; they are mild inducers [21].

Table 3 provides a brief summary of the pharmacokinetics and pharmacodynamics of antipsychotics, including the second-generation antipsychotics, for any approved indication in bipolar disorder, along with haloperidol, which is frequently mentioned by bipolar disorder guidelines. The table focuses on oral compounds, but DDIs of long-acting compounds are similar. A recent review compares the pharmacokinetics of oral and long-acting risperidone formulations [28]. Antipsychotics are not inducers. Some compounds can be mild to moderate CYP2D6 inhibitors: asenapine (from the second-generation compounds) and haloperidol (first generation).

Table 4 provides a brief summary of the pharmacokinetics and pharmacodynamics of the SSRIs. According to the guidelines, SSRIs are usually considered to be the antidepressants with less potential for causing switches to manic phases and the most recommended. Prior review articles described the pharmacokinetic and pharmacodynamic DDIs of other antidepressants with antipsychotics [14•] or AEDs [15•]. Some of the SSRIs are clinically relevant inhibitors of the metabolism of antipsychotics and some mood stabilizers.

Published Systematic Reviews of Combined Treatment in Bipolar Patients

Few systematic reviews focus on combined treatments during the manic, maintenance, or depressive phases.

Mania Three systematic reviews explore differences between monotherapy and combination therapy in mania in bipolar disorder [29•, 30•] or mania and bipolar depression [31•]. Ogawa et al. [29•] described mood stabilizers plus antipsychotic combination/augmentation therapy as (1) more effective than mood stabilizer monotherapy in terms of change in scores on mania rating scales at 3 weeks and at 1 week; (2) more effective than antipsychotic

Table 5 DDIs during manic phase of bipolar disorder in adult patients: no CBM but VPA is included (guidelines recommend discontinuation of antidepressants)

Lithium	VPA	APs (other are off-label)	Combinations
Narrow therapeutic window	*Inhibitor*: PAL, possible ASE *Inducer*: ARI *Possible inducer/inhibitor*: OLA	ARI CPZ[a] ASE HAL (off-label but well studied) PAL/RIS OLA QUE ZIP CAR *(up to 4 months to reach steady state)*	
ANTIMANIC EFFICACY			
Unknown *(one theory: ↓ protein kinase C activity)*	*Unknown* *(one theory: ↓ protein kinase C activity)*	*Possibly by D_2 blockade*	When monotherapy is not effective, combinations are thought to ↑ efficacy *(additive or synergistic pharmacodynamic effects)*
SEDATION: may help before antimanic efficacy starts and some tolerance may develop			
Unknown *Possibly dose-dependent*	*Unknown (↑ GABA activity)* *possibly dose-dependent*	*H_1 blockade* *dose-dependence and tolerance* Maximal: CPZ Lower: ZIP, QUE, OLA, ASE, HAL, RIS	Combinations (including with benzodiazepines) should ↑ sedation Benzodiazepines are frequently used *but tolerance develops rapidly* *(positive allosteric modulator of $GABA_A$ receptors)*
SAFETY			
Tremor			
Unknown postural or action *dose-related*	*Unknown* action and postural (< 2% parkinsonian symptoms)	*D_2 blockade at nigrostriatal system* *parkinsonian and dose-related* frequently associated with stiffness Maximum: FGAPs Second: RIS, PAL, LUR Third: ASE, OLA, ZIP Lower: QUE	↑ tremor by VPA-lithium and CBM-lithium Lithium may ↑ antipsychotic-induced tremor *by not-well-understood pharmacodynamic actions at dopaminergic system.*
Other neurological ADRs (cognitive deficits, cerebellar or confusion)			
Unknown *possibly dose-related*	*Unknown (↑ GABA activity)* *possibly dose-dependent*		↑ risk by VPA-lithium
Acute dystonic reactions			
		D_2 blockade at nigrostriatal system with rapid dose-related escalation FGAPs Rare in SGAPs except for RIS	Lithium may ↑ risk *by not-well-understood pharmacodynamic actions* CBM will not ↓ risk: *no relevant induction in first days*

Table 5 (continued)

Weight gain *Unknown* *possibly dose-related*	*Unknown*	*H_1 and 5-HT_{2C} blockade causes ↑ appetite* *possibly dose-related* *months or even > 1 year to plateau* Maximum: OLA Second: CPZ, ILO, PAL, QUE, RIS Third: ARI, ASE, HAL, LUR, ZIP	*Additive or synergistic pharmacodynamic effects are likely.*
Hyperlipidemia *Indirect: due to weight gain* *Direct: Not well studied* Case reports suggest it can ↑ triglycerides	*Indirect: due to weight gain* *Direct: unknown* ↓ total cholesterol and HDL	*Indirect: due to weight gain* *Direct effects on lipid metabolism* likely: CPZ, OLA, QUE possible: for others ↑ cholesterol and triglycerides	*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Hyperglycemia *Indirect: due to weight gain* *Direct: not important*	*Indirect: due to weight gain* *Direct: promote insulin resistance*	*Indirect: due to weight gain* *Direct effects on glucose metabolism* likely: CPZ, OLA, QUE possible: for others	*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Nausea and/or vomiting *Unknown* *early*: change formulation *late*: *possibly dose-related*	*Unknown* *possibly dose-related*	*D_2 blockers have antivomit effects* Initially ARI, LUR, ZIP can cause nausea	*Additive or synergistic pharmacodynamic effects are possible but have not been studied.* Consider lithium TDM.
Granulocytopenia *Not well understood* Granulocytosis	*Not well understood* Rarely granulocytopenia	*Not well understood* Rarely granulocytopenia	Lithium may attenuate granulocytopenia by other drugs. Some naturalistic studies suggest ↑ risk of granulocytopenia in combination of VPA-QUE.
Pancreatitis	*Not well understood* Rarely pancreatitis	*Not well understood* Very rarely pancreatitis	No studies on combined treatment. Be vigilant; it can be lethal.

Table 5 (continued)

Liver injury	*Toxic and/or immunological* Rare	OLA and more rarely other APs can cause ↑ enzymes CPZ can cause liver injury	No studies on combined treatment. Be vigilant; it can be lethal.
Neuroleptic malignant syndrome		*D2 blockade at nigrostriatal system but some other not-well-understood vulnerability factors may be important.*	Was described with FGAPs but has become very rare with SGAPs. Review articles suggest in many of the cases associated with SGAPs, lithium may be a contributing factor.

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

ADR adverse drug reaction, *AP* antipsychotic, *ARI* aripiprazole, *ASE* asenapine, *CAR* cariprazine, *CBM* carbamazepine, *CPZ* chlorpromazine, *D* dopamine, *DDI* drug-drug interaction, *FGAP* first-generation antipsychotic, *GABA* gamma-aminobutyric acid, $GABA_A$ gamma-aminobutyric acid A receptor, *H* histamine receptor, *HAL* haloperidol, $5\text{-}HT_{2C}$ serotonic 2c receptor, *HDL* high-density lipoprotein, *ILO* iloperidone, *LUR* lurasidone, *OLA* olanzapine, *PAL* paliperidone, *QUE* quetiapine, *RIS* risperidone, *SGAP* second-generation antipsychotic, *VPA* valproate, *ZIP* ziprasidone

[a] CPZ has US approval for mania. It is probably mainly metabolized by CYP2D6 and CYP1A2

monotherapy at 3 weeks, but not at 1 week; (3) no different from either monotherapy group in study withdrawal for any reason or due to ADRs; and (4) associated with more ADRs, especially with somnolence, while it did not increase treatment-emergent depression. Glue and Herbison [30•] described combined antipsychotic/mood stabilizer therapy as (1) significantly more effective than mood stabilizers or antipsychotic monotherapy for responder rate and (2) having the highest probability of being the best treatment based on change in mania rating scales and for response. Galling et al. [31•] described combined antipsychotic/mood stabilizers as associated with (1) significantly higher ADR burden when compared with mood stabilizer monotherapy, particularly weight-gain-related, extrapyramidal and metabolic ADRs and (2) significantly higher ADRs when compared with antipsychotic monotherapy with more risk for tremor, sedation, or vomiting.

As there are almost no RCTs [32, 33], carbamazepine has not been approved by the FDA for adjunctive treatment of mania. In 2003, the first RCT in which an antipsychotic, risperidone, was tested as an adjunctive treatment for mania was published [34]. Risperidone demonstrated adjunctive properties in the valproate and lithium arms but failed in the carbamazepine arm due to the induction of risperidone metabolism. It was unfortunate that the inductive properties of carbamazepine were not considered by the marketer and the risperidone dose was not doubled in the carbamazepine arm, which would probably make risperidone effective [35]. In a context of denial in the literature concerning the effects of inducers [35, 36], the pharmaceutical companies planning to market other antipsychotics for mania appeared to decide to exclude patients taking carbamazepine from RCTs and restrict them to patients on valproate or lithium. Only three other published RCTs included patients with combinations of carbamazepine and antipsychotics: (1) an international olanzapine RCT studying 60 patients allowed a high dose of olanzapine, up to 30 mg/day, to compensate for carbamazepine inductive effects [37], (2) a Japanese olanzapine RCT which recruited only one patient on carbamazepine and was discontinued [38], and (3) a carbamazepine RCT with 53 patients taking antipsychotics [39]. Thus, it is not surprising that two reviews of combined treatment in mania focused on combinations of antipsychotics with valproate or lithium but had to ignore those with carbamazepine [32, 33].

Maintenance In a 2011 meta-analysis, Vieta et al. indicated the data on combination therapies for the maintenance phase was very limited [40]. The complexity

Table 6 DDIs during manic phase of bipolar disorder in adult patients, including CBM but not VPA (guidelines recommend discontinuation of antidepressants)

Lithium	CBM	APs	Combinations
Narrow therapeutic window	*Powerful CYP/UGT inducer* *Auto-inducer: up to 3–5 weeks to reach maximum*	(Combinations with CBM are off-label) Regarding CBM: -Do not combine: CAR, LUR, QUE -3× dose: PAL -2× dose: ARI, HAL, OLA, RIS -ASE, CPZ[a]: unknown -ZIP: no dose change	BE CAREFULWITH CBM: CONSIDER TDMs CBM steady state requires 3–5 weeks and induction will be ↑ until steady state is reached. Consider AP TDM after 2–3 months of adding CBM.
ANTIMANIC EFFICACY			
Unknown (one theory: ↓ protein kinase C activity)	*Unknown (one theory: ↓ protein kinase C activity)*	*Possibly by D_2 blockade*	When monotherapy is not effective, combinations are thought to ↑ efficacy*(due to additive or synergistic pharmacodynamic effects)*
SEDATION: may help before antimanic efficacy starts and some tolerance may develop			
Unknown *possibly dose-dependent*	*↓ activity of voltage-dependent Na channels* *dose-dependent*	*H_1 blockade* *dose-dependence and tolerance* Maximal: CPZ Lower: ZIP, QUE, OLA, ASE, HAL, RIS	Combinations (including with benzodiazepines) should ↑ sedation. Benzodiazepines *(positive allosteric modulators of $GABA_A$ receptors)* are frequently used *but tolerance develops rapidly and can be induced with time by CBM.*
SAFETY			
Tremor			
Unknown postural or action *dose-related*		*D_2 blockade at nigrostriatal system* *parkinsonian and dose-related* frequently associated with stiffness Maximum: FGAP Second: RIS, PAL, LUR Third: ASE, OLA, ZIP Lower: QUE	↑ tremor by VPA-lithium and CBM-lithium. Lithium may ↑ antipsychotic-induced tremor *by not-well-understood actions at dopaminergic system.*
Other neurological ADRs (cognitive deficits, cerebellar or confusion)			
Unknown *possibly dose-dependent*	*↓ activity of voltage-dependent Na channels* *dose-dependent*		↑ risk by CBM-lithium.
Acute dystonic reactions			
		D_2 blockade at nigrostriatal system with rapid dose-related escalation FGAPs Rare in SGAPs except for RIS	Lithium may ↑ risk *by not-well-understood pharmacodynamic actions at dopaminergic system.*

Table 6 (continued)

Weight gain *Unknown* *possibly dose-related*	*Unknown*	*H_1 and 5-HT_{2C} blockade cause ↑ appetite* *possibly dose-related* Maximum: OLA Second: CPZ, ILO, PAL, QUE, RIS Third: ARI, ASE, HAL, LUR, ZIP	*Additive/synergistic pharmacodynamic effects are likely.* *Adding CBM is equivalent of ↓ AP dose*
Hyperlipidemia *Indirect: due to weight gain* *Direct: Not well studied* Case reports suggest it can ↑ triglycerides	*Indirect: due to weight gain* *Direct: induction of CYP* ↑ cholesterol and triglycerides	*Indirect: due to weight gain* *Direct effects on lipid metabolism* likely: CPZ, OLA, QUE possible: for others ↑ cholesterol and triglycerides	*Additive/synergistic pharmacodynamic effects are possible but have not been studied.*
Hyperglycemia *Indirect: due to weight gain* *Direct: not important*		*Indirect: due to weight gain* *Direct effects on glucose metabolism* likely: CPZ, OLA, QUE possible: for others	*Additive/synergistic pharmacodynamic effects are possible but have not been studied.*
Nausea and/or vomiting *Unknown* *early*: change formulation *late: possibly dose-related*	*↓ activity of voltage-dependent Na channels* *dose-dependent*	*D_2 blockers have antivomit effects* Initially ARI, LUR, ZIP can cause nausea	*Additive/synergistic pharmacodynamic effects are possible but have not been studied.* Consider lithium TDM.
Arrhythmias *↓ activity of voltage-dependent Na channels* *dose-dependent*	*↓ activity of voltage-dependent Na channels* *dose-dependent*		CBM-lithium: *↑ risk of sinus node dysfunction*
Hypothyroidism *Interferes with synthesis and release of thyroid hormones in several ways*	*Can ↓ free T_4 (rarely T_3) possibly by UGT induction*	Some data suggest QUE may interfere with thyroid function	CMB-lithium: *unclear if ↑ risk of hypothyroidism*
ADH *Blocks ADH action in kidney*	*↑ action and release of ADH*		Lithium ↓ risk of CBM-induced hyponatremia
Granulocytopenia *Not well understood* Granulocytosis	*Not well understood* Rarely granulocytopenia Risk of agranulocytosis	*Not well understood* Rarely granulocytopenia	Lithium may attenuate granulocytopenia by other drugs.

Table 6 (continued)

Neuroleptic malignant syndrome	*D_2 blockade at nigrostriatal system but some other not-well-understood vulnerability factors may be important.*	Was described with FGAPs but has become very rare with SGAPs. Review articles suggest in many of the cases associated with SGAPs, lithium may be a contributing factor.

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

ADH antidiuretic hormone, *ADR* adverse drug reaction, *AP* antipsychotic, *ARI* aripiprazole, *ASE* asenapine, *CAR* cariprazine, *CBM* carbamazepine, *CPZ* chlorpromazine, *D_2* dopamine 2, *DDI* drug-drug interaction, *FGAP* first-generation antipsychotic, *H_1* histamine-1 receptor, *5-HT_{2C}* serotonic 2c receptor, *$GABA_A$* gamma-aminobutyric acid A receptor, *H_1* histamine-1 receptor, *HAL* haloperidol, *ILO* iloperidone, *LUR* lurasidone, *Na* sodium, *OLA* olanzapine, *PAL* paliperidone, *QUE* quetiapine, *RIS* risperidone, *SGAP* second-generation antipsychotic, *TDM* therapeutic drug monitoring, *UGT* uridine 5′-diphospho-glucuronosyltransferase, *VPA* valproate, *ZIP* ziprasidone

[a] CPZ has US approval for mania. It is probably mainly metabolized by CYP2D6 and CYP1A2. CBM is probably a clinically relevant inducer of CPZ

of analyzing combined treatments can be understood if one realizes that some drugs appear to prevent mania (lithium and several antipsychotics) while others (lithium, lamotrigine, and quetiapine) may prevent depression [41]. In a 2014 review of RCTs and other studies, Bouli et al. proposed that combined treatments are associated with better efficacy but worse safety [42]. More recently, in 2016, Yathan et al. completed an RCT on the maintenance phase focused on adjunctive treatment with olanzapine or risperidone in patients taking lithium or valproate [43]. They found that risperidone or olanzapine adjunctive therapy for 24 weeks is beneficial, but continuation beyond this period may not be helpful since (1) risperidone does not reduce the risk of relapse, while (2) olanzapine's potential benefit needs to be weighed against an increased risk of weight gain.

Depression In 2013, Zhang et al. [44] completed a meta-analysis on the effects of antidepressants on response and switching to mania. Antidepressants were not associated with higher response or remission rates. In 2016, McGir et al. [45•], in their meta-analysis focused on bipolar depression, included six RCT trials adding second-generation antidepressants to mood stabilizers or antipsychotics. The combined treatment was associated with a small but significant improvement in clinician-rated depressive symptom score but no changes in remission rates versus placebo. There was no increased short-term risk of treatment-emergent mania or hypomania, but there was in the long-term at 52 weeks. McGir et al. [45•] proposed that antidepressants should be used only in the short term in bipolar patients. In conclusion, the treatment of bipolar depression is rather controversial [46] but, as efficacy of the various treatments is low, it clearly seems important to focus on avoiding ADRs [47].

Practical Guidelines for Clinicians Regarding DDIs in Adults with Bipolar Disorder

As combined therapy appears to be almost the norm for bipolar patients during the main three phases, mania, maintenance, and depression, one would think that the literature would provide easy sources for clinicians to find descriptions of the pharmacodynamic and pharmacokinetic DDIs in bipolar patients. Unfortunately, this is not the case. We are only aware of three prior articles aimed at summarizing pharmacokinetic and pharmacodynamic DDIs of pairs of drugs [13, 14•, 15•], and a recent review focused on the

Table 7 DDIs during maintenance treatment of adult patients with bipolar disorder (Level of evidence for CBM is low; it is not included for simplicity's sake)

Lithium	VPA	APs (other are off-label)	LTG	Combinations
Narrow therapeutic window	*Occasional patients*: *auto-induction* *Inhibitor*: PAL, possible ASE **CAREFUL with LTG** *Inducer*: ARI *Possible inducer/inhibitor*: OLA	ARI LAI RIS OLA QUE ZIP (CAR is different from other APs: up to 4 months to be eliminated)	No important effects on AP concentration **CAREFUL with VPA**	**Careful with VPA-LTG combination**
MOOD STABILIZER EFFICACY				
Unknown (one theory: suppressing inositol signaling)	*Unknown (one theory: suppressing inositol signaling)*	*Possibly by D_2 blockade*	*Unknown (one theory: down-regulation of arachidonic acid cascade[b])*	When monotherapy is not effective Combinations are thought to ↑efficacy. *(additive or synergistic pharmacodynamic effects)*
SEDATION: some tolerance may develop				
Unknown possibly dose-dependent	*Unknown (↑ GABA activity) possibly dose-dependent*	*H_1 blockade* *dose-dependence and tolerance* Lower: ZIP, QUE, OLA, ASE, HAL, RIS		*Additive or synergistic pharmacodynamic effects are likely.*
SAFETY				
Tremor				
Unknown postural or action *dose-related*	*Unknown* action and postural (<2% parkinsonian symptoms)	*D_2 blockade at nigrostriatal system* *parkinsonian and dose-related* frequently associated with stiffness Maximum: HAL Second: RIS, PAL, LUR Third: ASE, OLA, ZIP Lower: QUE	*Unknown*	↑ tremor by VPA-lithium and possibly LTG-lithium Lithium may ↑ antipsychotic-induced tremor *by not-well-understood pharmacodynamic actions at dopaminergic system.*
Other neurological ADRs (cognitive deficits, cerebellar or confusion)				
Unknown possibly dose-related	*Unknown (↑ GABA activity) possibly dose-dependent*			↑ risk by VPA-lithium
Weight gain				
Unknown possibly dose-related	*Unknown*	*H_1 and 5-HT_{2C} blockade cause ↑ appetite* *possibly dose-related* *months or even > 1 year to plateau* Maximum: OLA Second: PAL, QUE, RIS Third: ARI, ASE, HAL, LUR, ZIP		*Additive or synergistic pharmacodynamic effects are likely.*

Table 7 (continued)

Hyperlipidemia				
Indirect: *due to weight gain* *Direct*: *Not well studied* Case reports suggest it can ↑ triglycerides	*Indirect*: *due to weight gain* *Direct*: *unknown* ↓ total cholesterol and HDL	*Indirect*: *due to weight gain* *Direct effects on lipid metabolism* likely: OLA, QUE possible: for others ↑ cholesterol and triglycerides		*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Hyperglycemia				
Indirect: *due to weight gain* *Direct*: *not important*	*Indirect*: *due to weight gain* *Direct*: *promote insulin resistance*	*Indirect*: *due to weight gain* *Direct effects on glucose metabolism* likely: OLA, QUE possible: for others		*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Nausea and/or vomiting				
Unknown *early*: *change formulation* *late*: *possibly dose-related*	*↓ activity of voltage-dependent Na channels* *dose-dependent*	*D_2 blockers have antivomit effects* *Initially ARI, LUR, ZIP can cause nausea*	*↓ activity of voltage-dependent Na channels* *dose-dependent*	*Additive/synergistic pharmacodynamic effects are possible but have not been studied.* *Consider lithium TDM.*
Alopecia				
Unknown mechanism *(in some cases it may be due to hypothyroidism)*	*Unknown mechanism*			*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Osteoporosis				
In vitro *studies suggest ↑osteogenesis. and some clinical data indicate ↓ fracture risk*	*Mild inducer metabolism of Vitamin D*	*Hyperprolactinemia* Greater: HAL, PAL, RIS mild for others (ARI may ↑ prolactin)		No studies on combined treatment. Monitor for osteoporosis when using combinations for many years.
Risk of falls				
Ataxia *Unknown* *possibly dose-related*	Ataxia *Unknown (↑ GABA activity)* *possibly dose-dependent*	Orthostatic hypotension At onset or with ↑ dose Greater: QUE, RIS milder for others		Be careful in vulnerable patients, particularly in the elderly.
Granulocytopenia				
Not well understood Granulocytosis	*Not well understood* Rarely granulocytopenia	*Not well understood* Rarely granulocytopenia		Lithium may attenuate granulocytopenia by other drugs. Some naturalistic studies suggest ↑ risk of granulocytopenia in combination of VPA-QUE.

Table 7 (continued)

Liver injury	*Toxic and/or immunological* Rare	OLA and other APs only cause ↑ enzymes		No studies on combined treatment. Be vigilant; it can be lethal.
Stevens-Johnson syndrome	*Inhibits LTG metabolism*		*Associated with rapid titrations (more rarely after discontinuation of inducers).*	Follow dosing patterns from prescribing information. Combination with VPA requires halving: 1) titration and 2) maximum LTG dose.
Neuroleptic malignant syndrome		*D_2 blockade at nigrostriatal system but some other not-well-understood vulnerability factors may be important.*		Was described with FGAPs but has become very rare with SGAPs. Review articles suggest in many of the cases associated with SGAPs, lithium may be a contributing factor.

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

ADR adverse drug reaction, *AP* antipsychotic, *ARI* aripiprazole, *ASE* asenapine, *CBM* carbamazepine, *D_2* dopamine 2 receptor, *DDI* drug-drug interaction, *GABA* gamma-aminobutyric acid, *H_1* histamine-1 receptor, *5-HT_{2C}* serotonic 2c receptor, *HAL* haloperidol, *HDL* high-density lipoprotein, *LAI RIS* long-acting injectable risperidone, *LTG* lamotrigine, *LUR* lurasidone, *OLA* olanzapine, *PAL* paliperidone, *QUE* quetiapine, *RIS* risperidone, *SGAP* second-generation antipsychotic, *VPA* valproate, *ZIP* ziprasidone

pharmacodynamics of combinations of AEDs with antipsychotics, antidepressants and lithium [18••]. We have summarized for clinicians the limited published data, our research and clinical experience, and pharmacological knowledge of pharmacokinetic and pharmacodynamic mechanisms on DDIs in Tables 5, 6, 7, and 8. No attempt was made to grade the evidence since, unfortunately, the RCTs ignore the personalized approach required to study unusual subjects [48]; those patients having DDIs due to polypharmacy with three to four drugs are never going to be studied in RCTs. Tables 5 and 6 provide a summary of the potential for DDIs in the manic phase, without and with carbamazepine. Table 7 provides a summary of the potential for DDIs during the maintenance phase. Carbamazepine is not a first-line treatment according to the pharmacological guidelines and is excluded from Table 7 due to the high potential for the pharmacokinetic DDIs that are emphasized in Table 2. Table 8 provides a summary of the potential for DDIs during the depressive phase by adding the SSRIs.

Conclusions

These DDI tables (Tables 5, 6, 7, and 8) are attempts to be mainly practical and help clinicians remember and pay attention to frequent ADRs which should be expected in combined treatments of patients with bipolar disorder. They also include the most severe and potentially lethal ADRs that are so rare they will not be encountered in relatively small, short-term RCTs. As no article that we know has tried to develop such DDI tables in the context of polypharmacy, they are a first "baby step." These DDI tables will have to be improved in future articles, as more data can help us expand our personal insights and observations. Due to the extremely high frequency of polypharmacy, there is great need for studies of DDIs in bipolar disorder, but the lack of funding for clinical research is a major limitation. For increasing knowledge of DDIs, a collaborative effort is needed from all interested parties including (i) drug agencies and pharmaceutical companies, (ii) grant agencies, and (iii) researchers with expertise in (a) meta-analyses, (b) pharmacovigilance programs to detect DDIs, (c) DDI pharmacology, and (iv) clinicians treating patients with bipolar disorder.

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Table 8 DDIs during treatment of bipolar depression in adult patients with bipolar disorder (Guidelines offer limited agreement on the best choices)

Lithium	VPA	APs	LTG	ADs	Combinations
Narrow therapeutic window	*Occasional patients*: *auto-induction* *Inhibitor*: PAL, possible ASE **CAREFUL with LTG** *Inducer*: ARI *Possible inducer/inhibitor*: OLA	Only 3 approved: LUR OLA (with FLUO) QUE	No important effects on AP concentration **CAREFUL with VPA**	SSRIs *Relevant inhibitors*:[a] PAL/FLUO: potent CYP2D6 FLUO: weak to moderate of CYP2C19 CYP3A4 and moderate of CYP2C9	**Careful with VPA-LTG combination** *Remember some SSRIs are inhibitors*
POSSIBLE ANTIDEPRESSANT EFFICACY					
Unknown	*Unknown*	*Unknown*	*Unknown*	*Serotonin transporter reuptake inhibitors*	When monotherapy is not effective, combinations are thought to ↑ efficacy *(additive/synergistic pharmacodynamic effects)*
SWITCH TO MANIA					
				Do no prescribe ADs alone	It is thought that mood stabilizers ↓ risk of switching to mania when prescribing ADs
SEDATION: some tolerance may develop					
Unknown; *possibly dose-dependent*	*Unknown (↑ GABA activity)*; *possibly dose-dependent*	*H_1 blockade dose-dependence and tolerance* Higher: QUE, OLA			*Additive or synergistic pharmacodynamic effects are likely.*
SAFETY					
TREMOR					
Unknown postural or action *dose-related*	*Unknown* Action and postural (< 2% parkinsonian symptoms)	*D_2 blockade at nigrostriatal system* *Parkinsonian and dose-related* Frequently associated with stiffness Second after FGAP: LUR Third: OLA Lower: QUE	*Unknown*		↑ Tremor by VPA-lithium and possibly LTG-lithium. Lithium may ↑ AP-induced tremor *by not-well-understood pharmacodynamics actions at dopamine system.*
Akathisia					
		D_2 blockade at nigrostriatal system		*↓ Dopamine activity* Rare	*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Other neurological ADRs (cognitive deficits, cerebellar, or confusion)					
Unknown; *possibly dose-related*	*Unknown (↑ GABA activity)*; *possible dose-dependence*				↑ Risk by VPA-lithium
Weight gain					
Unknown; *possibly dose-related*	*Unknown*	*H_1 and 5-HT_{2C} blockade causes ↑ appetite*; *possibly dose-related months or even > 1 year to plateau* Maximum: OLA Second: QUE Third: LUR		*H_1 blockade causes ↑ appetite*; *possibly dose-related* PAR	*Additive or synergistic pharmacodynamic effects are likely.*

Table 8 (continued)

Hyperlipidemia				
Indirect: *due to weight gain* *Direct*: *Not well studied* Case reports suggest it can ↑ triglycerides	*Indirect*: *due to weight gain* *Direct*: *unknown* ↓ total cholesterol and HDL	*Indirect*: *due to weight gain* *Direct effects on lipid metabolism* Likely: OLA, QUE possible: for others ↑ Cholesterol and triglycerides	PAR *Indirect*: *due to weight gain*	*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
Hyperglycemia				
Indirect: *due to weight gain* *Direct*: *not important*	*Indirect*: *due to weight gain* *Direct*: *promote insulin resistance*	*Indirect*: *due to weight gain* *Direct effects on glucose metabolism* Likely: OLA, QUE possible: for others	PAR *Indirect*: *due to weight gain*	*Additive/synergistic pharmacodynamic effects are possible but have not been studied.*
Nausea and/or vomiting				
Unknown possibly dose-related	*Unknown possibly dose-related*	*D_2 blockers*: *antivomit effects* Initially LUR can cause nausea	*Serotonergic mechanisms*	*Additive/synergistic pharmacodynamic effects are possible but have not been studied.*
Sexual ADRs				
		Indirect: *due to hyperprolactinemia* *Direct effects*: *α blockade* Greater: OLA Possible: for others	*Serotonergic mechanisms*	*Additive or synergistic pharmacodynamic effects are possible but have not been studied.*
↑ QTc				
		Blocking of heart repolarizing potassium channels *Dose-related* Small risk for listed APs	*Blocking of heart repolarizing potassium channels* *Dose-related* Relevant for SSRIs	**A.** Be vigilant **B.** Consider ECG **C.** Torsades de pointes is rare but consider additive risk factors.
Anticholinergic (more properly antimuscarinic): including constipation and urinary retention				
		OLA and high-dose QUE are *antimuscarinic*	PAR: *antimuscarinic*	No studies on combined treatment.
ADH actions				
Blocks ADH action in kidney			↑ *Action and release of ADH in geriatric patients*	No studies on combined treatment.
Osteoporosis				
In vitro *studies suggest ↑osteogenesis, and some clinical data indicate ↓ fracture risk*	*Induced metabolism of vitamin D*	*Hyperprolactinemia* mild LUR, OLA, QUE (ARI may ↑ prolactin)	*Serotonergic mechanisms*	No studies on combined treatment. Monitor for osteoporosis when using it for many years.

Table 8 (continued)

Risk of falls					
Ataxia *Unknown; possibly dose-related*	Ataxia *Unknown (↑ GABA activity); possible dose-dependence*	Orthostatic hypotension at onset or with ↑ dose Greater: QUE Milder for other APs listed			Be careful in vulnerable patients, particularly in the elderly.
Risk of bleeding					
	Dose-related ↓ platelet count *Rarely coagulation impaired*			*↓ Serotonin in platelets*	Possible additive effects. Be careful during surgery or when co-prescribing other pro-hemorrhagic drugs.
Granulocytopenia					
Not well understood Granulocytosis	*Not well understood* Rarely granulocytopenia	*Not well understood* Rarely granulocytopenia			Lithium may attenuate granulocytopenia caused by other drugs. Some naturalistic studies suggest ↑ risk of granulocytopenia in combination of VPA-QUE.
Liver injury					
	Toxic and/or immunological Rare	OLA and other APs only cause ↑ enzymes			No studies on combined treatment. Be vigilant; it can be lethal.
Stevens-Johnson syndrome					
	Inhibits LTG metabolism		*Associated with rapid titrations (less often after discontinuation of inducers).*		Follow dosing patterns from prescribing information. Combination with VPA requires halving: (1) titration and (2) maximum LTG dose.
Serotonin syndrome					
↑ Serotonin activity				*Inhibitors of serotonin reuptake*	Be vigilant; it can be lethal.

Pharmacokinetic and pharmacodynamic mechanisms are described with italic letters in the table

AD antidepressant, *ADH* antidiuretic hormone, *ADR* adverse drug reaction, *AP* antipsychotic, *ARI* aripiprazole, *ASE* asenapine, *CYP* cytochrome, D_2 dopamine 2 receptor, *DDI* drug-drug interaction, *ECG* electrocardiogram, *FGAP* first-generation antipsychotic, *FLUO* fluoxetine, *FLUV* fluvoxamine, *GABA* gamma-aminobutyric acid, H_1 histamine-1 receptor, $5\text{-}HT_{2C}$ serotonic 2c receptor, *QTc* QT corrected interval, *QUE* quetiapine, *HAL* haloperidol, *HDL* high-density lipoprotein, *LTG* lamotrigine, *LUR* lurasidone, *OLA* olanzapine, *PAL* paliperidone, *PAR* paroxetine, *PKC* protein kinase C, *QUE* quetiapine, *RIS* risperidone, *SSRI* selective serotonin reuptake inhibitor, *VPA* valproate, *ZIP* ziprasidone

[a] We do not recommend using FLUV. If you decide to use FLUV, see Table 4 for its CYP inhibitory properties

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Fornaro M, De Berardis D, Koshy AS, Perna G, Valchera A, Vancampfort D, et al. Prevalence and clinical features associated with bipolar disorder polypharmacy: a systematic review. Neuropsychiatr Dis Treat. 2016;31(12):719–35. **Systematic review of the high frequency of polypharmacy in bipolar disorder.**
2. Goldberg JF, Brooks JO 3rd, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, et al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J Clin Psychiatry. 2009;70(2):155–62. https://doi.org/10.4088/JCP.08m04301.
3. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30(6):495–553. https://doi.org/10.1177/0269881116636545.
4. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15(1):1–44. https://doi.org/10.1111/bdi.12025.
5. Fountoulakis KN, Grunze H, Vieta E, Young A, Yatham L, Blier P, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int J Neuropsychopharmacol. 2017;20(2):180–95. https://doi.org/10.1093/ijnp/pyw109.
6. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry. 2013;14(3):154–219. https://doi.org/10.3109/15622975.2013.770551.
7. National Institute for Health and Clinical Excellence. Bipolar disorder (update): the management of bipolar disorder in adults, children and adolescents in primary and secondary care. (Clinical Guideline 185.) 2014. http://guidance.nice.org.uk/CG185.
8. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49(12):1087–206. https://doi.org/10.1177/0004867415617657.
9. Ostacher MJ, Tandon R, Suppes T. Florida best practice psychotherapeutic medication guidelines for adults with bipolar disorder: a novel, practical, patient-centered guide for clinicians. J Clin Psychiatry. 2016;77(7):920–6. https://doi.org/10.4088/JCP.15cs09841.
10. Kanba S, Kato T, Terao T, Yamada K, Committee for Treatment Guidelines of Mood Disorders, Japanese Society of Mood Disorders, 2012. Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2012. Psychiatry Clin Neurosci. 2013;67(5):285–300. https://doi.org/10.1111/pcn.12060.
11. de Leon J. A critical commentary on the 2017 AGNP consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology. Pharmacopsychiatry. 2018;51(1-02):63-68. https://doi.org/10.1055/s-0043-117891.
12. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic Clin Pharmacol Toxicol. 2007;100(1):4–22. https://doi.org/10.1111/j.1742-7843.2007.00017.x.
13. de Leon J, Santoro V, D'Arrigo C, Spina E. Interactions between antiepileptics and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2012;8(3):311–34. https://doi.org/10.1517/17425255.2012.660918.
14.• Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2014;10(5):721–46. **First attempt to explore pharmacokinetic and pharmacodynamic drug-drug interactions between new antipsychotics and new antidepressants.** https://doi.org/10.1517/17425255.2014.885504.
15.• Italiano D, Spina E, de Leon J. Pharmacokinetic and pharmacodynamic interactions between antiepileptics and antidepressants. Expert Opin Drug Metab Toxicol. 2014;10(11):1457–89. **First attempt to explore pharmacokinetic and pharmacodynamic drug-drug interactions between antiepileptic and antidepressant drugs.** https://doi.org/10.1517/17425255.2014.956081.
16. Spina E, Hiemke C, de Leon J. Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2016;12(4):407–22. https://doi.org/10.1517/17425255.2016.1154043.
17.• Spina E, Pisani F, de Leon J. Clinically significant pharmacokinetic drug interactions of antiepileptic drugs with new antidepressants and new antipsychotics. Pharmacol Res. 2016;106:72–86. **This review article includes tables with a summary of dose correction factors for the pharmacokinetic drug-drug interactions used in the tables of this new article.** https://doi.org/10.1016/j.phrs.2016.02.014.
18.•• Spina E, de Leon J. Potentially clinically relevant pharmacodynamics interactions between antiepileptic drugs and psychotropic drugs: an update. Curr Pharm Des. 2017;23 https://doi.org/10.2174/1381612823666170809102258. **First attempt to explore pharmacodynamic drug-drug interactions of antiepileptic drugs with the main psychiatric drugs.**
19. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51(1-02):e1. https://doi.org/10.1055/s-0043-116492.
20. Lana F, Martí-Bonany J, Fuster J, de Leon J. Reduction in serum concentration of valproic acid secondary to the intake of ibuprofen as an example of valproic acid auto-induction metabolism. Actas Esp Psiquiatr. 2016;44(4):136–44.
21. de Leon J. The effects of antiepileptic inducers in neuropsychopharmacology, a neglected issue. Part I: a summary of the current state for clinicians. Rev Psiquiatr Salud Ment. 2015;8(2):97–115. https://doi.org/10.1016/j.rpsm.2014.10.006.
22. de Leon J. The effects of antiepileptic inducers in neuropsychopharmacology, a neglected issue. Part II: pharmacological issues and further understanding. Rev Psiquiatr Salud

Ment. 2015;8(3):167–88. https://doi.org/10.1016/j.rpsm.2014.10.005.
23. Zamani A, Omrani GR, Nasab MM. Lithium's effect on bone mineral density. Bone. 2009;44(2):331–4. https://doi.org/10.1016/j.bone.2008.10.001.
24. Jin Y, Xu L, Hu X, Liao S, Pathak JL, Liu J. Lithium chloride enhances bone regeneration and implant osseointegration in osteoporotic conditions. J Bone Miner Metab. 2017;35(5):497–503.
25. Finley PR. Drug interactions with lithium: an update. Clin Pharmacokinet. 2016;55(8):925–41. https://doi.org/10.1007/s40262-016-0370-y.
26.• Roux M, Dosseto A. From direct to indirect lithium targets: a comprehensive review of omics data. Metallomics. 2017;9(10):1326–51. https://doi.org/10.1039/c7mt00203c. **Comprehensive update of complex lithium pharmacodynamic actions.**
27. Jackson J, McCollum B, Ognibene J, Diaz FJ, de Leon J. Three patients needing high doses of valproic acid to get therapeutic concentrations. Case Rep Psychiatry. 2015;2015(542862):1–12. https://doi.org/10.1155/2015/542862.
28. Schoretsanitis G, Spina E, Hiemke C, de Leon J. A systematic review and combined analysis of therapeutic drug monitoring studies for long-acting risperidone. Expert Rev Clin Pharmacol. 2017;10(9):965–81. https://doi.org/10.1080/17512433.2017.1345623.
29.• Ogawa Y, Tajika A, Takeshima N, Hayasaka Y, Furukawa TA. Mood stabilizers and antipsychotics for acute mania: a systematic review and meta-analysis of combination/augmentation therapy versus monotherapy. CNS Drugs. 2014;28(11):989–1003. **Systematic review of combined therapy versus monotherapy in mania.** https://doi.org/10.1007/s40263-014-0197-8.
30.• Glue P, Herbison P. Comparative efficacy and acceptability of combined antipsychotics and mood stabilizers versus individual drug classes for acute mania: network meta-analysis. Aust N Z J Psychiatry. 2015;49(12):1215–20. **Systematic review of combined therapy versus monotherapy in mania.** https://doi.org/10.1177/0004867415614109.
31.• Galling B, Garcia MA, Osuchukwu U, Hagi K, Correll CU. Safety and tolerability of antipsychotic-mood stabilizer co-treatment in the management of acute bipolar disorder: results from a systematic review and exploratory meta-analysis. Expert Opin Drug Saf. 2015;14(8):1181–99. **Systematic review of combined therapy versus monotherapy in mania or bipolar depression.** https://doi.org/10.1517/14740338.2015.1053457.
32. Lin D, Mok H, Yatham LN. Polytherapy in bipolar disorder. CNS Drugs. 2006;20(1):29–42. https://doi.org/10.2165/00023210-200620010-00003.
33. Geoffroy PA, Etain B, Henry C, Bellivier F. Combination therapy for manic phases: a critical review of a common practice. CNS Neurosci Ther. 2012;18(12):957–64. https://doi.org/10.1111/cns.12017.
34. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. Br J Psychiatry. 2003;182(02):141–7. https://doi.org/10.1192/bjp.182.2.141.
35. de Leon J. False-negative studies may systematically contaminate the literature on the effects of inducers in neuropsychopharmacology: part II: focus on bipolar disorder. J Clin Psychopharmacol. 2014;34(3):291–6. https://doi.org/10.1097/JCP.0000000000000115.
36. de Leon J. False-negative studies may systematically contaminate the literature on the effects of inducers in neuropsychopharmacology. Part I: focus on epilepsy. J Clin Psychopharmacol. 2014;34(2):177–83. https://doi.org/10.1097/JCP.0000000000000093.
37. Tohen M, Bowden CL, Smulevich AB, Bergstrom R, Quinlan T, Osuntokun O, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. Br J Psychiatry. 2008;192(2):135–43. https://doi.org/10.1192/bjp.bp.107.041301.
38. Katagiri H, Takita Y, Tohen M, Higuchi T, Kanba S, Takahashi M. Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder. Curr Med Res Opin. 2012;28(5):701–13. https://doi.org/10.1185/03007995.2012.666961.
39. Weisler RH, Kalali AH, Cutler AJ, Gazda TD, Ginsberg L. Safety of carbamazepine extended-release capsules used in combination with other psychotropic medications for the treatment of bipolar I disorder. Psychiatry (Edgmont). 2008;5(5):49–60.
40. Vieta E, Günther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, et al. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol. 2011;14(8):1029–49. https://doi.org/10.1017/S1461145711000885.
41. Popovic D, Reinares M, Amann B, Salamero M, Vieta E. Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder. Psychopharmacology. 2011;213(4):657–67. https://doi.org/10.1007/s00213-010-2056-8.
42. Buoli M, Serati M, Altamura AC. Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review. J Affect Disord. 2014;152-154:12–8. https://doi.org/10.1016/j.jad.2013.08.024.
43. Yatham LN, Beaulieu S, Schaffer A, Kauer-Sant'Anna M, Kapczinski F, Lafer B, et al. Optimal duration of risperidone or olanzapine adjunctive therapy to moo stabilizer following remission of a manic episode: a CANMAT randomized double-blind trial. Mol Psychiatry. 2016;21(8):1050–6. https://doi.org/10.1038/mp.2015.158.
44. Zhang Y, Yang H, Yang S, Liang W, Dai P, Wang C, et al. Antidepressants for bipolar disorder: a meta-analysis of randomized, double-blind, controlled trials. Neural Regen Res. 2013;8(31):2962–74. https://doi.org/10.3969/j.issn.1673-5374.2013.31.009.
45.• McGirr A, Vöhringer PA, Ghaemi SN, Lam RW, Yatham LN. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138–46. **Systematic review of combined therapy versus monotherapy in bipolar depression.** https://doi.org/10.1016/S2215-0366(16)30264-4.
46. Köhler S, Gaus S, Bschor T. The challenge of treatment in bipolar depression: evidence from clinical guidelines, treatment recommendations and complex treatment situations. Pharmacopsychiatry. 2014;47(2):53–9. https://doi.org/10.1055/s-0033-1364004.
47. Ketter TA, Miller S, Dell'Osso B, Calabrese JR, Frye MA, Citrome L. Balancing benefits and harms of treatments for acute bipolar depression. J Affect Disord. 2014;169(Suppl 1):S24–33. https://doi.org/10.1016/S0165-0327(14)70006-0.
48. de Leon J. Evidence-based medicine versus personalized medicine: are they enemies? J Clin Psychopharmacol. 2012;32(2):153–64. https://doi.org/10.1097/JCP.0b013e3182491383.