

THE PSYCHIATRY LETTER

Table of Contents

Special article:

Antipsychotics (dopamine blockers) for bipolar depression

Study of the month:

Symbyax dissected

Drug of the month:

Quetiapine

Psychopathology:

"Mixed depression"

Case of the month:

A mixed depression suicide

Curbside consults:

Questions and cases from you

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"Depression" that isn't just depression

Welcome to the second issue of the Psychiatry Letter.

This issue has a main theme: use of antipsychotic agents in mood conditions. The case of antipsychotics in bipolar depression is an excellent case example of the PL approach to psychiatry. In the extensive special article on this topic, we examine the scientific evidence, and think outside of the boxes set by the pharmaceutical industry and the Food and Drug Administration (FDA). Good clinical practice isn't as simple as just following FDA indications, which doesn't mean FDA indications don't matter. We need to interpret FDA indications in the context of looking at the scientific literature ourselves, and drawing our own conclusions. That's what PL is here to help you to do.

The treatment of bipolar depression with agents that aren't standard "antidepressants" also raises the question of the meaning of "depression." In this issue, we discuss the concept of "mixed depression", or depression with psychomotor excitation and sometimes frank manic symptoms. This kind of depression doesn't improve, and may worsen, with antidepressants, while it improves with antipsychotics and mood stabilizers. Understanding mixed states of depression is key to knowing when to use antidepressants versus antipsychotics; and it's not all about whether bipolar illness is present or not.

We end with a case where not making these distinctions can have tragic consequences.

If you are one of our inaugural subscribers, thank you for continuing this journey with us into a new psychiatry of the future. If you are newly joining us, we hope you find new ideas that can help you improve your practice.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Antipsychotics (dopamine blockers) in bipolar depression* FDA indications don't tell the whole story

FDA-indicated medications for acute bipolar depression are quetiapine (Seroquel), olanzapine-fluoxetine combination (Symbyax, also called OFC), and most recently lurasidone (Latuda). PL holds the view that two medications which do not have FDA indications, ziprasidone (Geodon) and aripiprazole (Abilify), also have a scientific rationale for efficacy in bipolar depression.

Of these agents, quetiapine and OFC have, by far, the worst risks, especially if used long-term (given that they worsen metabolic syndrome and cardiovascular risks). Thus, *PL recommends lurasidone, aripiprazole, and ziprasidone - not quetiapine or OFC - as the primary dopamine blocker treatments for bipolar depression.* The rest of this article will explain this recommendation.

Dopamine blockers, not “antipsychotics”:

It's illogical to speak of “antipsychotics” for bipolar depression. Most cases of bipolar depression don't involve psychotic symptoms (delusions or hallucinations). So why do we speak of “antipsychotics” for non-psychotic bipolar depression? Drug companies will tell you: Well, there are “antidepressant effects” to antipsychotics; or, worse: antipsychotics are also antidepressants.

Readers of George Orwell will recognize here his dystopic vision of a “Newspeak” that abuses language for other purposes. This is not just PL's opinion. The European College of Neuropsychopharmacology (ECNP) and the American College of Neuropsychopharmacology (ACNP) recently convened a task force on

psychiatric drug nomenclature where they draw the conclusion that the names we use for our drugs are scientifically incorrect and clinically misleading (Zohar et al 2014). Orwell said it long ago: Thought is constrained by language. *If we use false terms, we'll have false thoughts.*

So let's stop using the phrase “antipsychotic” (or “antidepressant”, for that matter; PL will address that topic in a future issue). “Antipsychotics” are not just effective for psychotic symptoms; they have many other non-psychotic uses: for depressive symptoms, anxiety, sleep, agitation in dementia or delirium, even physical states like emesis. The ECNP/ACNP task force recommends using clinically neutral terms based on biological mechanisms. PL

recommends the general term “dopamine blocker” for this class of agent. (Biological definitions have their own limitations, we realize: drugs have more than one mechanism, and they differ on potencies for any mechanism; see PL website).

By changing our language, we'll immediately realize that these agents aren't limited to “psychotic” conditions. Hence their utility in (non-psychotic) bipolar depression.

Acute bipolar depression:

Studies using dopamine blockers exist mainly for *acute* bipolar depression, meaning a current severe clinical depressive episode that usually lasts 1-6 months untreated. The usual duration of treatment, in standard FDA studies, is 6-8 weeks.

“PL recommends lurasidone, aripiprazole, and ziprasidone - not quetiapine or OFC - as the primary dopamine blocker treatments for bipolar depression.”

Thus, to the extent there is scientific evidence of efficacy of dopamine blockers in bipolar depression, that evidence exists for about 2 months of treatment. That's it. Not 2 years. And certainly not 20 years.

In other words, this research evidence, if valid, would instruct you to treat bipolar depression with dopamine blockers for two months, and *then stop those agents*. To say that dopamine blockers should be continued, we would need evidence of maintenance efficacy of these agents. It is worth pointing out that there are no data on OFC for maintenance treatment (olanzapine is not the same), and that the aripiprazole maintenance study found that it was *not* effective in prevention of bipolar depressive episodes (efficacy was present only in prevention of manic episodes). Thus, *long-term preventive efficacy cannot be assumed from acute efficacy data*.

Olanzapine-fluoxetine combination (Symbyax): The Study of the Month dissects the data behind OFC. As described there, that study proved that olanzapine did *not* work for treating bipolar depression, and the amount of data supportive of OFC is rather small in size and less definitive than you might believe.

Quetiapine (Seroquel): Acute bipolar depression studies with quetiapine are, superficially, more straightforward than with OFC. Astra Zeneca planned two large 8 week trials of quetiapine alone versus placebo, and the drug worked in both cases, with large effect sizes of benefit that included core mood symptoms (like anhedonia, low energy, and sad mood). The FDA provided the bipolar depression indication.

As clinicians and patients know, quetiapine is an extremely sedating drug. It has potent antihistaminic, antiadrenergic, and anticholinergic effects. One would tend to notice taking it. Some academic leaders involved in the quetiapine studies acknowledge that it's likely that those RCTs weren't truly blinded: Patients could tell when they took quetiapine, and when they didn't (received placebo). Unblinded studies tend to increase treatment effect sizes, hence the quetiapine studies likely overestimate its benefits.

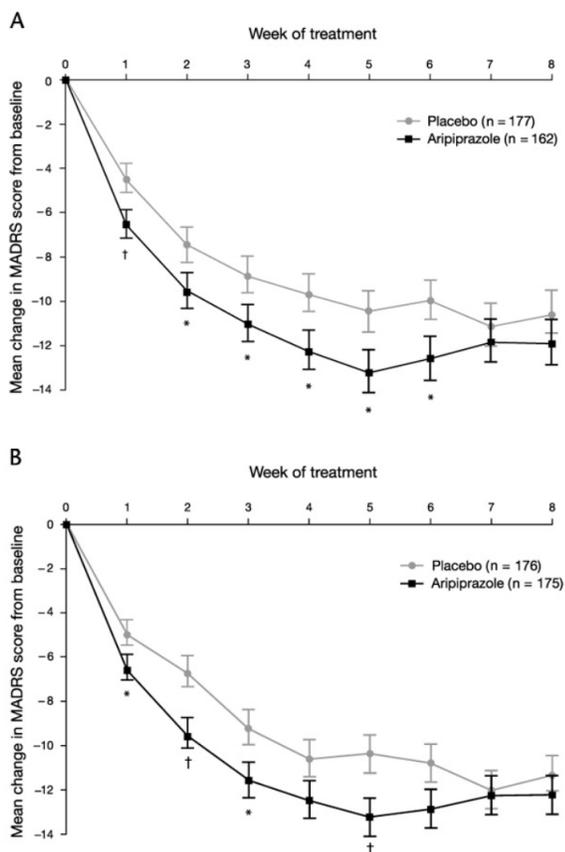
This doesn't mean quetiapine isn't effective in bipolar depression at all. It means that the claim that it is *especially* effective, more so than other agents, may be inflated based on sedating non-mood effects.

In sum, quetiapine showed benefit; but *is it as big of a clinical benefit as it seems, or an inflated effect of a highly sedating drug?*

Lurasidone (Latuda): The newest FDA-indicated agent, was shown effective in two 6-week RCTs of bipolar depression. It isn't sedating, and other aspects of study design seem valid. Of the three agents with FDA indications, this one seems to have the most valid scientific proof.

Aripiprazole (Abilify): Now we come to agents without FDA approval for bipolar depression. Let's begin with aripiprazole. Bristol Myers Squibb did two 8 week trials of this agent for bipolar depression. In both cases, repeatedly, the drug was better than placebo from weeks 1 through 6, but at week 8, placebo showed a benefit which reduced the overall effect size and led to a p-value above 0.05 (not statistically significant). (See figures: MADRS= Montgomery Asberg Depression Rating Scale). FDA indication

wasn't given since the study was designed with the a priori outcome of improvement at 8 weeks.



The PL viewpoint is that aripiprazole was effective in bipolar depression, because the benefits seen at 4 and 6 weeks are more meaningful scientifically than the final 8 week endpoint. This is why: *The duration of a study should be adjusted to the duration of an illness.* There is no general rule that a study should be long, or that the longer the study, the better it is. Mania RCTs are only 3 weeks in duration, because manic episodes are short, lasting 2-4 months untreated according to some studies. Unipolar depression studies are 8 weeks long because unipolar depressive episodes are long, lasting 6-12 months untreated. But bipolar depressive episodes, though longer than mania, are shorter than unipolar depressive episodes. According to a

century of natural history data dating back to Kraepelin, bipolar depressive episodes tend to last 2-6 months, less in those with rapid-cycling course (about one-quarter of bipolar subjects). So, if you conduct a trial that is 8 weeks long, in a condition where a substantial minority of patients is improved by 1-3 months, you will have a “placebo” rate of improvement, due to natural remission, that is high. This makes it difficult to show drug benefit. Thus 6 weeks is more scientifically valid than 8 weeks for the duration of a bipolar depression trial. The PL editor made this point to Bristol Myers Squibb when it planned the original bipolar depression study. That mistake has confused some clinicians into thinking the drug has no benefit for a condition in which it showed benefit. This is why the lurasidone studies were 6 weeks long. And this is why the aripiprazole study's effect at 4 and 6 weeks shouldn't be ignored.

If aripiprazole improves depressive symptoms, it isn't surprising that other studies found it to be effective in unipolar depression, leading to FDA indication as augmentation of antidepressants.

Lastly, although PL strongly believes that biological rationale should not be the primary factor in treatment decisions, biological mechanisms are relevant for interpreting clinical trial data. Aripiprazole is a moderate dopamine agonist. Dopamine agonists (like amphetamines and bupropion) improve depressive symptoms. In contrast, olanzapine and quetiapine have little monoamine agonist effects (minor effects were shown retrospectively in some animal studies later conducted by their companies), and certainly not as much as aripiprazole (or ziprasidone).

Ziprasidone (Geodon): Based on biological mechanism, if any dopamine blocker is going to be effective for depressive symptoms, it should be ziprasidone. It's the only modern dopamine

blocker that also is a serotonin reuptake inhibitor (SRI) and a norepinephrine reuptake inhibitor (NRI). Its effects are about equally as potent as standard SRI and tricyclic antidepressants. The trouble is that Pfizer conducted two RCTs of ziprasidone versus placebo in acute bipolar depression, and it didn't work. Unlike aripiprazole, there wasn't benefit at some weeks but not others. There just wasn't benefit.

This should seem odd: Drugs without strong monoamine agonism, like quetiapine, are supposedly "antidepressant" in their effects, while drugs with strong classic antidepressant mechanisms, like ziprasidone, are not. How can this be?

Perhaps it serves to come back to clinical concepts.

"Bipolar depression" just means a current "major" depressive episode in someone with past mania/hypomania. As with "major" depressive episodes in unipolar depression, it may represent multiple different depressive subtypes, as discussed in the PL website. One relevant subtype is "mixed depression", i.e., depression mixed with manic symptoms. It could be that the apparent "antidepressant" effect of dopamine blockers has to do partly with dopamine blockade itself, which is effective for mixed manic/depressive states, rather than with mood elevating monoamine agonism effects of classic SRIs/ NRIs. In other words, dopamine blockade provides benefit for mixed states - this is well known. *Most "bipolar depression" is, in fact, a mixed state*, as described in the Psychopathology article. Hence almost any dopamine blocker should help, not just quetiapine or OFC.

This hypothesis could be tested directly by studying ziprasidone (or any antipsychotic) in patients selected for "mixed depression". The PL

editor designed and conducted this project and indeed ziprasidone was effective, better than placebo, in an overall sample of 73 subjects.

This result is similar in size to the OFC study arm (n=86). In other words, the widespread use of OFC is based on an amount of scientific evidence that is similar to what exists with ziprasidone for mixed depression. Pfizer never sought FDA indication for mixed depression efficacy because ziprasidone was about to become a generic medication when this study was completed (hence there were no profit to be gained by marketing this use). If clinicians only went by FDA indications, they would ignore ziprasidone, not because efficacy data don't exist, but because there weren't economic motivations to obtain FDA indication for them.

The case of ziprasidone and OFC shows why clinicians should focus on science, not primarily presence or absence of FDA indications.

Low doses: William Osler's axiom was that all drugs are toxic; it's only the dose and indication which makes them therapeutic. In the aripiprazole studies of bipolar depression, secondary analyses found that in those treated with *lower* doses (5-10 mg/d), aripiprazole was *more* effective than placebo; it was in the higher dose group (>10 mg/d) that placebo seemed similar to aripiprazole. In the lurasidone monotherapy studies, the low dose arm (20-60 mg/d; mean dose 32 mg/d) was equivalent in efficacy to the high dose arm (80-120 mg/d; mean dose 82 mg/d). It is the PL clinical experience that a similar principle may apply with ziprasidone. At low doses (<80 mg/d), we've seen patients show good improvement for bipolar depression; it could be that *higher* doses are *less* effective. This observation seems to contradict common clinical intuitions: *we tend to believe that more is better*. But

this isn't always the case. A biological explanation may be as follows: At lower doses of all dopamine blockers, there is less dopamine blockade. It's commonly believed that about 80-90% dopamine blockade is needed for full antipsychotic effect. That's great, but we're not treating psychosis here; we're treating mostly non-psychotic bipolar depression. It could be that only about 50% or so of dopamine blockade is sufficient to get benefit for the mixed depressive state in bipolar depression. Thus, higher doses of dopamine blockers may confer no further mood benefit. Turning to the dopamine agonism of aripiprazole and the serotonin/norepinephrine reuptake blockade of ziprasidone, *these effects are present to the same extent at any dose, including low doses.*

So it could be that low doses provide a good amount of "antidepressant"-like monoamine agonism, with sufficient dopamine blockade for manic symptoms. While higher doses might just produce more and more dopamine blockade, which might just produce more antimanic effect, moving the mood down, rather than elevating it.

These biological explanations may or may not be correct, but as we said in issue 1, the PL approach is to emphasize the clinical research evidence, which indicates *more* benefit in bipolar depression with *lower* doses of dopamine blockers. *We encourage clinicians to avoid using the high doses shown effective for schizophrenia and mania as their standard for treating bipolar depression.*

Weighing risks and benefits: Osler's dictum that the art of medicine is the art of balancing probabilities also comes into play. Clinicians shouldn't just use those drugs which are FDA-indicated, and hence marketed to them. They should compare the scientific evidence of all

drugs, take into account comparisons of side effects among drugs with scientific evidence of efficacy, and then weigh probabilities of benefits versus harms. As discussed on the PL website, quetiapine has notable and long-term metabolic syndrome and harmful cardiovascular effects. So does olanzapine. When these known common harms are taken into account, the benefit/harm calculation tilts in the direction of lurasidone, aripiprazole, and ziprasidone.

These three agents are left mainly with the risk of akathisia (discussed in detail on the PL website), which can present as worsened agitation and/or suicidality. (Note: We are aware that other side effects exist with these agents, such as QT prolongation with ziprasidone, but those risks are less frequent than akathisia, which is the most common reason for dropout and serious adverse events in practice. See the PL website for further

"Clinicians should avoid using the high doses shown effective for schizophrenia and mania as their standard for treating bipolar depression"

discussion of why QT prolongation is not the major problem with ziprasidone.) Akathisia is clinically

dangerous and immediate intervention is needed, either by stopping the dopamine blocker, or by lowering its dose and/or adding a counteracting agent. Among counteracting agents, PL experience and a limited scientific literature suggest that beta-blockers are the most effective, especially propranolol, which best crosses the blood-brain barrier. In the US, a generic slow-release formulation, propranolol ER, is now available without insurance restrictions. We recommend it to be given at night, since its benefits extend throughout the day. Doses begin at 60 mg/d. Pulse should be followed so it doesn't fall below 60 beats/minute. In healthy middle-aged persons, the propranolol ER dose range for akathisia tends to be 60-120 mg/d.

How to dose:

- Lurasidone: Give 20 mg at night for 2-3 weeks. Increase to 40 mg at night if there's no benefit at all. In a minority of cases, consider going to 60 mg/d. Remember: higher doses above 60 mg/d were *not* more effective in the monotherapy RCTs of bipolar depression, where the mean effective dose was around 30 mg/d. A common mistake is to use higher doses, like 60-120 mg/d, based on FDA labeling for schizophrenia, not bipolar depression.
- Aripiprazole: Begin with 2 mg at night for 2-3 weeks. If there's no effect, increase to 5 mg at night for 2-3 weeks. If there's no effect, increase to 7.5 mg at night for 2-3 weeks. If there's no effect, increase to 10 mg at night. Higher doses than 10 mg/d are proven less effective for bipolar depression than lower than 10 mg/d. Thus there is no reason to use more than 10 mg/d. Again, a common mistake is to go up to 20-30 mg/d based on FDA labeling for schizophrenia or mania, not bipolar depression.
- Ziprasidone: Begin with 20 mg at night for 2-3 weeks. If there's no effect, increase to 40 mg at night for 2-3 weeks. If there's no effect, increase to 20 mg in the morning and 40 mg at night for 2-3 weeks, then if needed increase to 40 mg twice daily. In the PL experience, higher than 80 mg/d doesn't tend to produce more efficacy for bipolar depression. Instead, akathisia increases with higher doses.

If patients develop akathisia despite having some benefit, PL recommends propranolol ER 60 mg at night, increasing as needed to 80-120 mg at night. If there's no or little benefit with one of these agents, and akathisia occurs, we recommend stopping the current drug and using another. If akathisia occurs with multiple dopamine blockers, we recommend *pre-treatment* with propranolol ER 80-120 mg at night *before* starting a different dopamine blocker trial.

The PL Bottom Line

- PL recommended agents for bipolar depression are lurasidone, aripiprazole, and ziprasidone.
- Low doses should be used. Akathisia is the main problem with these agents. Propranolol ER can be used to manage that problem in some cases.
- The benefit of quetiapine is probably overestimated in its studies.
- Olanzapine alone is proven ineffective.
- Dopamine blockers may mostly help "bipolar" depression when it represents "mixed depression", the combination of severe depression with some manic symptoms.

Selected References: J Zobar et al, European Neuropsychopharmacology, 2014, 24: 1005-1014. ME Thase et al, Aripiprazole monotherapy in nonpsychotic bipolar I depression, Journal of Clinical Psychopharmacology, 2008, 28: 13-20. A Patkar et al, A 6 week randomized double-blind placebo-controlled trial of Ziprasidone for the acute depressive mixed state. . PLoS One. 2012;7(4):e34757. A more complete reference list and links are available in this article on the PL website.

PL Reflection

We will develop better new drugs but it will be a continual challenge for doctors to learn how to properly use them. Otherwise it would be like giving a driver's license to someone who can't drive.

Frank J. Ayd, Jr MD 2005

Study of the month: *Symbyax dissected*

Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression.

M Tohen et al, Arch Gen Psychiatry 2003; 60: 1079-1088

When side effects masquerade as efficacy

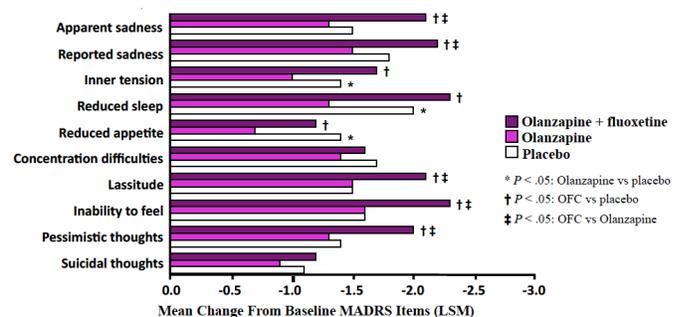
The PL editor was once invited by Eli Lilly to present the main results of this OFC study at the annual meeting of the American Psychiatric Association. Speaking to a large audience, the PL editor noted that the “OFC” (olanzapine/fluoxetine combination) study was designed originally to prove efficacy of olanzapine alone, not OFC. The study was powered statistically for that purpose: 370 subjects were randomized to olanzapine and 377 to placebo. Luckily for the manufacturer, a small sample of 86 subjects also was randomized to OFC. Olanzapine alone showed benefit over placebo using p-values, but the “effect size” was tiny: a very small improvement in the Montgomery Asberg Depression Rating Scale (MADRS) of about two points: one for sleeping more and another for eating more (see figure). Sedation and increased appetite are side effects of olanzapine, not proof of efficacy for bipolar depression. The PL editor made these points; he was never invited by that company to give a lecture again.

In the published paper, the company and its 7 academic coauthors begin the conclusion section of the abstract with a first sentence that is technically true but clinically false: “Olanzapine is more effective than placebo....” Later in the paper, they have to admit absence of effect on core mood symptoms, but that admission was buried in the text. Clinicians continue to have the false impression, a decade later, that olanzapine alone is effective in bipolar depression.

It isn't.

The FDA reached the same conclusion. Olanzapine was shown *not* to be effective in acute bipolar depression, despite its “statistically significant” benefit over placebo. In contrast, OFC showed efficacy, including for standard mood symptoms of sad mood and low interest and low energy, albeit in a small sample of 86 subjects.

Bipolar Depression – OFC MADRS Item Analyses



Tohen et al 2003

Should a drug get an FDA indication when its only data involve less than 100 subjects treated in the effective arm in one randomized clinical trial? Usually, the general FDA rule is that companies need to show efficacy in two randomized clinical trials before an indication will be given. Exceptions are made, though, especially for clinical conditions in which few or no treatments already are approved. This was the case for acute bipolar depression in 2003. No FDA indications existed at that time for any drug. (Keep in mind that “antidepressants” are not FDA-indicated as having efficacy for bipolar depression).

So the FDA gave approval for OFC based on one RCT, with a small sample, even though the study was never designed for that purpose! Now that two other agents are approved for bipolar depression, if the same OFC data were presented to the FDA today, the FDA probably would reject it as insufficient to be given an indication for bipolar depression. But OFC is now grandfathered into its FDA indication. And, going by the mere fact of FDA indication, many clinicians will assume that the scientific evidence for efficacy of OFC in bipolar depression is as good as quetiapine or lurasidone. It isn't.

The PL Bottom Line

- Olanzapine alone is proven ineffective for acute bipolar depression.
- OFC's efficacy is based on a small sample.
- OFC has the same problems with long-term metabolic and cardiovascular harm as exist with olanzapine.
- There is no evidence of long-term efficacy or safety with OFC in prevention of depressive episodes in bipolar illness.

Drug of the Month: Quetiapine (Seroquel)

Sedating, but not much of a dopamine blocker

Clinicians of a certain age will remember thioridazine (Mellaril). At low doses, it helped sleep and reduced anxiety; at higher doses where it helped psychosis or mania, it knocked people out. But at least it wasn't a benzodiazepine, and it didn't have as much extrapyramidal side effects as other neuroleptic agents, especially at low doses. So clinicians loved it. And so did many patients.

Quetiapine is the Mellaril of the 21st century. Unlike thioridazine, it has very minimal risk of

tardive dyskinesia, so it has proved a natural replacement for a drug which clinicians can give to patients for that inevitable request: Doctor, please give me something to help me sleep (or in another variant, to help me be less anxious). Benzodiazepines are the class of medication for those uses, of course, but their potential dependence limits their use in some people. Hence the never-ending search for the holy grail of the benzodiazepine-like drug which doesn't cause addiction. Hence quetiapine.

Fast Facts: Quetiapine

Typical effective dose: 50-150 mg/d for anxiety or insomnia, 200-300 mg/d for bipolar depression, 300-400 mg/d for mania, 300-800 mg/d for psychosis/schizophrenia

Biological mechanism: Mild dopamine blockade

Typical side effects: Sedation, weight gain, metabolic syndrome/ cardiovascular harms, diabetes, akathisia

Less common but important side effects: orthostatic hypotension

Clinically proven efficacy: acute bipolar depression, acute mania, schizophrenia,

Questionable efficacy: unipolar depression, anxiety, maintenance prevention of bipolar mood episodes

Clinical efficacy and inefficacy

The popularity of quetiapine isn't about schizophrenia, although this medication is listed among "antipsychotics", as described above. PL will focus on the many other uses of this drug, besides schizophrenia. The special article above discusses bipolar depression. Quetiapine also was studied for generalized anxiety disorder and major depressive disorder, and some benefit reportedly

was seen at low doses (< 200 mg/d), but FDA reviewers were reluctant to give FDA indication for those uses given concerns about medical harms from widespread use in the primary care setting. Efficacy in acute mania has been shown in standard studies. Efficacy in maintenance prevention of bipolar illness has been shown using randomized discontinuation trial designs, which may have questionable validity (see PL website).

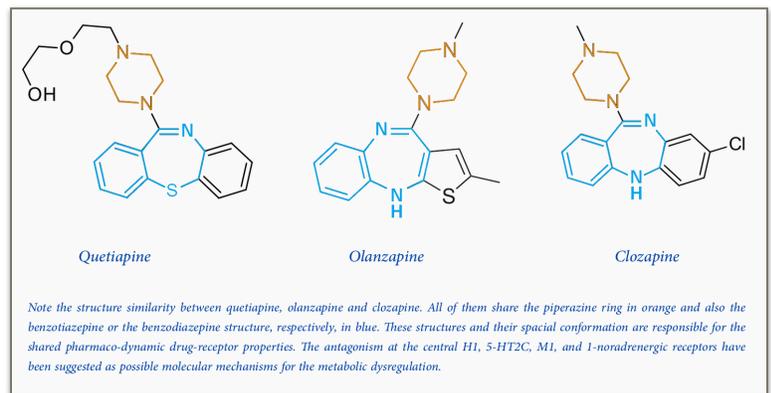
Biological mechanism

Although it's called an "antipsychotic", quetiapine is different from other treatments for psychosis in that it never reaches, at any dose, more than mild amounts of dopamine blockade. From about 400 mg/d to 800 mg/d, there is a plateau of about 30-40% D₂ receptor blockade, nowhere near the 80-90% D₂ blockade obtained with all other antipsychotics except clozapine (see PL website).

Side Effects

Sometimes, similarity of chemical structure entails similar side effects. Quetiapine's basic chemical structure is similar to clozapine and olanzapine (see Figure). All three have notable antihistamine, anticholinergic and antiadrenergic effects, all of which add up to marked sedation. Importantly, all share the major harm of metabolic syndrome: increasing susceptibility to hypertension, diabetes, and hyperlipidemia. All these are major cardiovascular risk factors. Separate from these direct physiological effects

(decreasing insulin sensitivity), quetiapine *also* causes weight gain, which further worsens these cardiovascular risk factors. Regarding neuroleptic effects, quetiapine can cause akathisia, although apparently less frequently than other dopamine blockers (based on the CATIE study); it doesn't cause much parkinsonism because its inherent anticholinergic effects reduce parkinsonian symptoms; tardive dyskinesia is rare.



The PL Bottom Line

- Quetiapine is a mild dopamine blocker.
- It is effective in bipolar depression, mania, and schizophrenia; sedation effects may be interpreted as mood and psychosis benefits
- Long-term efficacy in bipolar illness can be questioned based on study design questions.
- Benefits for anxiety/insomnia/agitation likely relate to antihistamine/antiadrenergic/anticholinergic effects.
- It causes metabolic syndrome, worsens cardiovascular risks, & has notable weight gain.

Selected reference on biological mechanism: E Richelson, Receptor pharmacology of neuroleptics: Relation to clinical effects. J Clin Psychiatry. 1999;60 Suppl 10:5-14.

PL Reflection

Treatment is pruning a rose of its thorn.

Jeffrey Gilbert MD

Psychopathology: *Mixed depression*

Depression with psychomotor excitation is not just a 'major depressive episode'

Clinicians use the word "depression" loosely. The DSM concept of a "major depressive episode" combines very different kinds of depressive states: Take melancholia: there is no reactivity of mood, which means that the patient is just plain sad all the time - not angry or anxious or anything else. There is marked anhedonia, meaning the patient has basically no interests at all, and is often unable to get out of bed or function at all. Now take its opposite: "mixed depression", where the patient has highly reactive mood, ranging from very sad to very angry to very anxious to very agitated; there is decreased interest but patients can still function somewhat.

"Major" depression isn't really one thing: it includes many things, including types of depression that can be completely opposite in their symptoms.

Does this matter, practically? It may. If agitated, labile, angry "mixed depression" is different than the slowed down, sad, anhedonic "melancholia", they may have different treatments. European researchers, often less influenced by DSM, have been studying the concept of mixed depression a great deal in recent decades. They've shown that it occurs more commonly in bipolar than unipolar depression, that it

seems to respond especially well to dopamine blockers (neuroleptics), and that it worsens with antidepressants.

In one study of over 5000 depressed patients, Angst and colleagues reported that 47% of DSM-defined "major depressive" episodes included 3 or more DSM manic symptoms. This was the case even with DSM-defined "major depressive disorder", not just bipolar disorder. In other words, *about half of depressive episodes in major depressive disorder involve multiple manic symptoms, i.e., are mixed depressive states.*

This may seem odd: how can you have

"major depression" with three manic symptoms? It happens because DSM doesn't allow you to diagnose mania or hypomania unless those manic symptoms occur for 4 or more days. But these "mixed depressed" states often involve consistent depression, with bursts of manic symptoms for a few hours or a day or two. DSM says: Ignore those manic symptoms; they didn't happen. Just diagnose a major depressive episode. Yet those

are exactly the kind of agitated, labile depressive states that seem to respond to dopamine blockers.

As importantly, if we give antidepressants to those agitated, labile, angry depressed patients, they seem to

"There is a kind of depression where...patients also have psychomotor excitation: they are angry, revved up at times, sometimes high in libido, and very agitated."

Koukopoulos' mixed depression criteria

- A DSM-defined major depressive episode
- At least 3 of 8 items:
 - Psychic agitation or inner tension
 - Racing or crowded thoughts
 - Irritability or unprovoked rage
 - Absence of retardation
 - Talkativeness
 - Dramatic description of suffering or frequent spells of weeping
 - Mood lability or marked reactivity
 - Early insomnia

get *more* agitated, labile, and angry. This sometimes ends in suicide, which may explain why some depressed patients get *more* suicidal on antidepressants (see the Case of the Month below and the PL website on this controversial topic).

In short, there is a kind of depression where, despite being sad and low in interest and energy and sometimes suicidal, patients also have psychomotor excitation: they are angry, revved up at times, sometimes high in libido, and very agitated. In other words, *some manic-like symptoms are mixed into the depressive state.*

This concept of mixed depression was organized into diagnostic criteria by the late Athanasios Koukopoulos, the leading thinker, clinician, and researcher in this field (see Table).

The PL Bottom Line

- About one-half of all depressive episodes, irrespective of whether the overall mood diagnosis is bipolar or unipolar, involve "mixed depression".
- These psychomotor excited mixed depressive states worsen with antidepressants and improve with dopamine blockers.

Further reading: A. Koukopoulos. Melancholia agitate and mixed depression. Acta Psychiatr Scand Suppl. 2007;(433): 50-7. J. Angst et al, Prevalence of undiagnosed bipolar disorder in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry. 2011 Aug;68(8): 791-8. A. Koukopoulos and Angst articles A Koukopoulos and SN Gbaemi. The primacy of mania. Eur Psychiatry. 2009 Mar;24(2):125-34.

Case of the month:

A mixed depressive suicide

A 69 year-old male seeks treatment for severe depression. He had experienced one depressive episode 30 years earlier, leading to psychiatric

hospitalization and improvement after one month of treatment with imipramine. He remained well for three decades without any psychotropic medication treatment. He was a successful journalist, writing a number of books; he was passionate, liberal, and opinionated, often having some interpersonal conflicts with those who had different political views. He possessed a wide circle of friends, and an equally wide circle of enemies. He raised three adult children, was divorced, remarried, and happy in his current relationship. He had partially retired five years earlier, but was still writing, traveling, and enjoying his activities. He was normally high in energy, slept about 6 hours nightly, had many activities, high libido, and was very creative.

In March, he began to feel inexplicably sad, with low energy and decreased interest in his usual activities. His libido remained high and active, though, and when he would have a good day, he would describe pleasurable sexual activity with his wife. He was also agitated and anxious and worried about being depressed again after decades of wellness. He was more angry than usual.

Family history was positive for severe depression in some relatives but no one sought help and no official diagnoses or treatments existed. The patient had no drug allergies and no drug/alcohol abuse. His medical history was normal except for mild hyperlipidemia.

He visited his primary care doctor who prescribed sertraline 25 mg/d. He immediately felt better for a few days, but then became more depressed again. Sertraline was increased to 50 mg/d. He improved for a few days, then felt worse again. Sertraline was increased to 100 mg/d. He then felt high in his mood, with markedly increased energy, very high libido, and a complete inability to sleep. He called a friend and complained about this mood state: it was uncomfortably energetic and

he was worried about not sleeping at all. After two days, these symptoms went away and he went back into his depressive state. His primary care doctor consulted DSM-5 and concluded that since those symptoms had lasted two, not four, days, they didn't represent a hypomanic episode. Since they had gone away and the patient remained very depressed, his doctor increased sertraline to 150 mg/d and consulted a psychiatrist.

The patient had investigated the topic on the internet, had read about antidepressant-induced mania/hypomania as representing possible bipolar illness, and told the psychiatrist that he was willing to take lithium for his current depression. The psychiatrist told the patient that the diagnosis was major depressive disorder and that lithium wasn't necessary.

Over the next three months, the psychiatrist increased sertraline to 200 mg/d, added bupropion plus lorazepam, and gave brief trials of quetiapine 25 mg for sleep, venlafaxine in place of sertraline (added to bupropion), and trazodone for sleep. The patient had no further brief hypomanic-like episodes, but his depression didn't improve, and he became more and more agitated and angry. He was taken to the emergency room a few times by his wife due to concerns about some expression of suicidal ideation, but he would always deny imminent intent or plan, and would refuse voluntary hospitalization. He wasn't hospitalized. One morning he hung himself.

The PL diagnosis and clinical impression

The PL diagnosis is a mixed depressive episode. Using DSM definitions, the patient can't be diagnosed with bipolar illness because the hypomanic episode lasted two days, not four. Yet *he clearly had multiple manic symptoms. Thus he meets the definition of "mixed depression".*

He was never offered lithium or dopamine blockers (except low dose quetiapine for sleep) so we can't know if those agents would have helped him. But PL would have recommended at least low dose lithium for his suicidality (see PL website) and some dopamine blocker (like aripiprazole) for his overall mixed depression.

It's clear that antidepressants didn't improve his mixed depression, and they may have worsened it, hastening its suicidal conclusion.

The PL Bottom Line

- Manic symptoms during depression, lasting less than four days, were ignored.
- "Mixed depression" was present and didn't improve with multiple antidepressants.
- Lithium or dopamine blockers weren't offered for mixed depression because of over-reliance on identifying a DSM-defined bipolar diagnosis.
- Suicide was the result either of lack of efficacy of antidepressants for mixed depression, or antidepressant-related worsening of the mixed depressive state.

"Using DSM definitions, the patient can't be diagnosed with bipolar illness...yet he clearly had multiple manic symptoms. Thus he meets the definition of 'mixed depression.'"

PL Reflection

Our first reaction after a suicide is surprise. Our second reaction is: Well, *of course* it happened....
 The gap between the two reactions is the paradox of suicide. *Leston Havens MD*

Curbside consults:

Questions and cases from you

Question: In the first issue of PL, you discussed bupropion but you didn't mention its use in ADHD. What is your perspective on that topic?

PL: We emphasized that bupropion is a mild amphetamine, so it isn't surprising that it works for ADHD. We used to recommend bupropion for ADHD as a presumably non-amphetamine agent. Since this isn't the case, PL has no special preference for bupropion in ADHD.

Question: I have an 80 year old attorney patient, treated with lorazepam 1 mg BID. Is that acceptable? Should I be concerned about anything in particular, like falls or hip fracture?

PL: For every year of life, renal function declines by about 1%. By age 80, people have 50% less renal function than at age 30. So 2 mg/d at age 80 is like 4 mg/d at age 30. That's why doses should

be cut in half in the elderly. Generally, PL suggests not exceeding 2 mg/d lorazepam long-term in younger adults, or 1 mg/d in the elderly. Not only are there risks of poor coordination and falls, but also delirium and possibly dementia, since cognition also is impaired. It's best, in sum, to minimize benzodiazepines in the elderly.

Question: What should we tell patients about taking ziprasidone with food?

PL: Its manufacturer recommends that ziprasidone be taken with about 500 calories of food to maximize absorption. Otherwise, it's about half less absorbed. Some patients find this onerous, especially if they worry about weight gain. The clinical relevance is that you may need to prescribe a higher dose for the same effect if patients don't take it with food. PL recommends that ziprasidone be taken with some food, but we don't insist upon it, since PL recommends titrating dose to clinical effect in any case.

Clinical tip of the month: Give lithium for suicidal symptoms, even at low dose.

In the case of the month, lithium was avoided in a suicidally depressed individual because DSM-defined bipolar illness couldn't be diagnosed. Lithium is the only psychotropic drug shown to prevent completed suicide based on randomized studies. Blood levels and doses are based on mania efficacy, not suicide prevention. Multiple studies of lithium in drinking water indicate anti-suicide benefits at doses that would be considered trace in clinical practice, equivalent to about 1 mg/d. In the experience of PL editors, and based on these studies, *any dose of lithium may help prevent suicide*. Consider giving suicidal patients 150-300 mg/d of lithium carbonate, or even less with lithium citrate, for suicide prevention. These doses are unlikely to cause major medical problems or blood level toxicity. But they may save a life. (Sources: S. Mauer et al, Australian and New Zealand Journal of Psychiatry, 2014, 48: 809-818. A. Cipriani et al, BMJ. 2013; 346:f364)

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