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Review Article

# Perils of Pragmatic Psychiatry: How We Can Do Better

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## Abstract

Etiologic and pathophysiologic understanding of psychiatric disorders is still in its early stages. The neurobiology of major psychiatric disorders has yet to be fully elucidated. Psychiatric diagnoses are often based on presenting symptoms, lacking reliability and stability. For a variety of reasons, many notable laboratory and clinical observations have not been tested in large trials. Lacking this validation, these potentially valuable practices have not been widely disseminated nor translated into real world practice. Pragmatic practice today requires optimum use of the available resources. This may sometimes require translating novel treatments supported by strong, evidence-based, level II evidence; but still lacking level I evidence into practice and greater utilization of evidence-based approved practices. The purpose of this paper is to highlight some common avoidable pitfalls in practice, and to offer a few psychopharmacological pearls.

**Keywords:** Alcohol; Anxiety; Bipolar; Depression; Insomnia; Pragmatic psychiatry; Psychiatry practice; Psychopharmacology; Schizophrenia; Substance; Suicide; Treatment; PTSD

## Introduction

Etiologic and pathophysiologic understanding of psychiatric disorders is still in early stages. Psychiatric diagnoses are often based on less reliable and inconsistent symptoms, rather than biological markers. Although standard psychiatric diagnostic systems and criteria exist for many disease processes, the imprecise utilization of such diagnostic concepts, by many practitioners, lead to unfortunate clinical consequences.

For a variety of reasons, many significant advances in neuroscience, pre-clinical studies, and phase 2 proof-of-concept studies have not been further studied or validated in large-scale trials. Thus, they have not translated to routine clinical practice. Furthermore, many other meaningful clinical observations may never be subject to high quality Randomized Controlled Trials (RCTs) or other large-scale higher quality evidence-based medicine. As such, current psychiatric practice relies on too few evidence-based treatments of modest effectiveness; rather than those, if further explored, would be more effective treatments.

Facing these realities, pragmatic psychiatric practice today requires optimal use of the resources available. This means more accurate applications of adequately studied diagnostic concepts, more widespread use of the evidence-based approved practices, and increased familiarity with novel and potentially helpful treatments. Granted however, that such treatments should themselves be based on available pre-clinical and lower quality clinical evidence (observational case reports, case series, open label trials, small RCTs) as shown in figure 1.

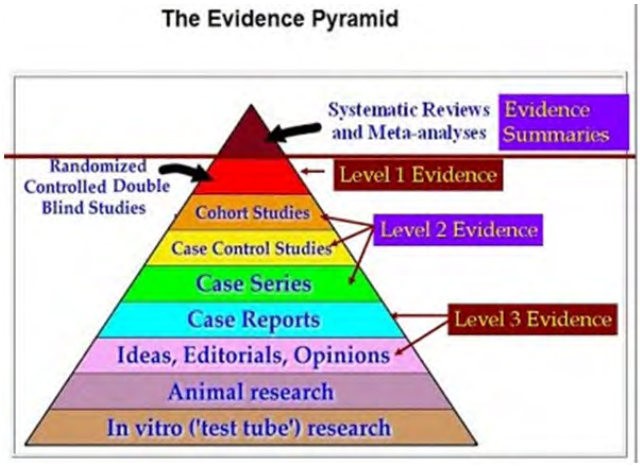


**Figure 1:** Rating System for the Hierarchy of Evidence.

Meta-analyses and systematic reviews are important and useful; they are not usually considered "level I" evidence. Reviews may reflect reviewer bias. Meta-analyses are most useful when relatively homogeneous studies lacked statistical power to separate active treatments.

The purpose of this paper is to highlight some common pitfalls encountered in the practice of psychiatry, as well as to relay potential issues in making correct diagnoses. Some important, pragmatic, psychopharmacological "pearls" are also included; to potentially aid in the improvement of psychiatric practice.

## Common Imprecision in Assessment and Diagnosis

### Schizophrenia and related psychoses

Clinicians often record both the diagnoses of schizophrenia and schizoaffective disorder, and schizoaffective disorder, bipolar type and bipolar I with psychosis concurrently in the same patient. Assuming that further evaluation is needed to clarify between the two, the differential diagnosis should be added as a rule out diagnosis. Having both diagnoses documented together may reflect imprecise thinking or at least, imprecise record keeping. The diagnosis of schizoaffective disorder is often made incorrectly because it lacks diagnostic reliability and stability [1]. One of the criteria for schizoaffective disorder is that a major mood episode be present for the majority

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(more than 50% of the time) of the total duration of the illness. This is not an easy history to elicit from patients and family. This makes eliciting a good history from patients and family, and correlating it with past medical records vital to establishing the diagnosis. Evaluating the state versus trait phenomena, and incorporating it into the interview process may also make it easier and more likely to arrive at the more appropriate diagnosis [2]. For example, in bipolar I with psychosis, psychosis is a state phenomenon; whereas in schizophrenia, psychosis is a trait phenomenon. In reality, this may not be always easy to tease out but it is worth trying. In practice, because schizophrenia is often associated with depressive symptoms, it can be treated with an antidepressant; similar to schizoaffective disorder, depressive type. In the future, schizoaffective disorder, depressive type diagnosis can be dropped while schizoaffective disorder, bipolar type may be labeled as schizophrenia with predominant bipolar features.

## Imprecise diagnosis of bipolar disorder and mood lability

Patients often describe their mood in the terms "it is up and down all the time. One minute I am up, and the next minute I am down." This may be due to their belief that these shifts qualify them for a diagnosis of bipolar disorder. Clinicians should probe the patient's history adequately to clarify and assess whether, in fact, they fulfill the criteria for hypomania or mania. For example, with diligence, past psychiatric hospitalizations or arrests with jail time may be revealed by the patient. If such history is compatible with a manic episode, it may indicate severe behavioral disturbances associated with a bipolar I diagnosis.

By definition, mood lability refers to oscillations between feelings of euphoria and feelings of depression, anxiety, irritability, rage, or another strong emotion. Mood lability can be present in a variety of conditions including mood disorders, personality disorders, substance withdrawal states, or even delirious states. Hence, the term "mood lability" is nonspecific, and is often difficult to interpret when encountered in a patient's history. This term is being overused as the primary indication for treatment, and is seen more frequently since "mood lability" has been set up as a default indication in many electronic medical record templates. Specifically, because mood stabilizers and Second Generation Antipsychotics (SGAs) are often prescribed on the basis of mood lability, it becomes imperative that the underlying conditions be clarified. If possible, the exact indications for each medication should be tied to those conditions rather than the broad indication of mood lability. If the term "mood lability" is not used accurately, it becomes a non-specific, potentially misleading term of limited value in evaluating the patient. Greater attention to definitional accuracy will not only limit over-prescription of medication, but also improve communication among clinicians in practice.

## Mood disorder

In contrast to the previous discussion on misdiagnosing, many times, it is the sheer number of concurrent diagnoses that pose a problem. There can be 2-3 unspecified diagnoses (some as rule out diagnoses) entered for a patient; thus prompting a cocktail of antidepressants, mood stabilizers, antipsychotics and anxiolytics to treat him or her. Sometimes these regimens may be necessary in patients presenting with a wide array of symptoms unresponsive to simple medical regimens. However, with multiple diagnoses showing overlapping symptoms, and increasingly complex drug combinations; clinicians may have a hard time distinguishing which symptom, associated with which disorder, he or she may be treating. In this regard, utilizing a more dimensional approach may be the answer.

Disruptive Mood Dysregulation Disorder (DMDD) is another example of the need for accurate diagnoses and differentials. Clinicians are too often diagnosing DMDD using only the DSM-5 A-E criteria. The often overlooked G criterion for DMDD states that the categorical diagnosis should not be made for the first time in a patient before age 6 or after age 18. This alarming incidence of patients being incorrectly diagnosed with DMDD may be related, as mentioned earlier, to imprecise diagnosing, or to the inadequate categorical system of diagnosing. Sometimes, in addition to assessing and assigning a categorical diagnosis, patients must also be analyzed with the dimensional approach. The exclusive use of the categorical diagnosis and underutilization of the dimensional assessment prompts any outlier symptom, not fitting into the syndromal diagnosis, to be added as a footnote. Commonly, with long term follow up and evaluation, these outliers become more relevant, and the diagnosis clearer. For example, when patients are dimensionally diagnosed with major depression and bipolar disorder, it becomes redundant to add unspecified anxiety as a diagnosis; as symptoms of anxiety are commonly associated with these two diagnoses. The cross-cutting symptoms of DSM-5 may, in the future, resolve this issue.

## Assessing comorbidities in substance use disorders

Several patients with Substance Use Disorder (SUD) have a Co-occurring Disorder (COD). In a registry-based study, the prevalence of SUD was 25.1% in schizophrenia, 20.1% in bipolar disorder and 10.9% in depressive illness [3]. In the CATIE study, 37% people with schizophrenia also had current SUD [4]. In the International Consortium in Psychiatric Epidemiology study in people with SUD, 35% and 45% of the population had a mood and an anxiety disorder respectively [5]. A distinction must be made between the true diagnosis of SUD and unspecified mood/psychotic disorder and SUD seen with Major Depressive Disorder (MDD), bipolar II, and other diagnoses. In the latter case, SUD is a COD. In such cases, clinicians tend to separately diagnose the SUD and further diagnose accompanying mental health disorders, such as unspecified schizophrenia, unspecified bipolar or unspecified depression.

Consider the case of SUD and depression. It is imperative to ascertain whether the patient's episodes of depression led to the substance use or vice versa. Patients can provide insight as to whether their depressive episodes are entirely due to substance use by recalling if their clinical depression persists for long periods of time when they are abstinent. This is crucial, as there is no evidence to suggest that an antidepressant or a mood stabilizer is effective in substance induced mood disorder [6]. Abstinence is the treatment of substance induced mood disorder. An antidepressant is indicated only if there is MDD independent of SUD. Treating substance induced depression with an antidepressant is comparable to treating adjustment disorder with an antidepressant, which is not indicated. In treating the anxiety symptoms associated with SUD, buspirone and sertraline [7,8] have been shown to have better outcomes [9].

SUDs are also commonly linked to Posttraumatic Stress Disorder (PTSD). Among people seeking help for the treatment of SUD, 30-50% have either lifetime or current PTSD diagnosis [10-13]. In 46 male Veterans, who were inpatients with SUD, 77% had severe childhood trauma, and 58% had lifetime PTSD. The total number of lifetime SUDs was significantly associated with childhood trauma experience [14]. In 95 inpatients with SUD, the prevalence of current

crime-related PTSD was 38% [15]. The prevalence of PTSD in Alcohol Use Disorder (AUD) can be up to 63% [16]. Unfortunately, PTSD is often not detected and is under diagnosed by clinicians [15].

### Changes from DSM-IV to DSM-5

The addition of new diagnoses and criteria in DSM-5, like DMDD, was discussed earlier. Although controversial, these criteria have elicited change, intended or unintended, within clinical practice. However, the changes to diagnostic qualifiers in DSM-5 to "unspecified" from the DSM-IV's "not otherwise specified" have not had its intended effect in clinical practice. Clinicians continue to use the term "unspecified" excessively and inappropriately for many patients. Furthermore, DSM-5, in many cases, created some inadvertent complexities in classifying diagnoses. For example, "Other specified schizophrenia spectrum and other psychotic disorder" and "unspecified schizophrenia spectrum and other psychotic disorder" both can fall under "unspecified psychosis." Even substance induced psychosis has to be diagnosed with one of these; bringing in the term "schizophrenia" in the diagnosis is unnecessary and inappropriate. These new classifications hinder patient education, and many clinicians must often refer back to DSM-5 to recall the diagnoses if it cannot be found within their hospital electronic medical record. An example of this is apparent in the SUD diagnosis discussed previously. Mild SUD is defined as having 2-3 symptoms, moderate SUD as having 4-5 symptoms, and severe SUD as having more than 6 out of 11 symptoms. In clinical practice, however, the checklists needed to classify this diagnosis are seldom completed thoroughly. The differentiation of mild, moderate or severe SUD is made based more on quick gestalts and intuition.

## Pharmacological Treatment: Perils and Pearls

Patient Health Questionnaire (PHQ-9) has been used successfully in psychiatric practice to target dimensions and monitor prognosis. There is evidence that its use has led to better outcomes [17-20]. Proper medication review and optimal medical management is another way to improve patient outcomes. For many patients, combination pharmacological treatment, often referred to as "polypharmacy" is the rule rather than exception. What clinicians are attempting to do by this practice is to increase their chances of successfully targeting different symptoms, by addressing multiple mechanisms of action concurrently. Rather, combination treatment should only be considered when attempted monotherapy is only partially effective, and/or when the diagnoses are associated with multiple neurotransmitters. This approach may be warranted in several cases, as many symptoms in psychiatric disorders are associated with more than one neurotransmitters.

### Medication selection

Clinicians generally pay closer attention to safety and tolerability issues than cost factors and patient education on dosing. These considerations are especially important with regard to patient adherence. Many patients are unlikely to take medications that require multiple doses or produce unpleasant side effects throughout the day. Almost all psychotropics produce sedation and somnolence. Thus, they may be more likely to be adhered to regularly by patients if prescribed to be used at bedtime once daily. PRN medications, however, may be used for daytime anxiety or agitation, and judicious daytime dosing is appropriate in stabilizing acute psychotic or manic patients. Furthermore, medications such as aripiprazole, bupropion and stimulants that have insomnia as a side effect are best prescribed in the morning. Although dosing standing medications 2-4 times per day is a common practice in inpatient settings, where patients commonly present in a manic or psychotic state; upon stabilization and discharge, all medications should ideally be given at bedtime. Even when the available medications allow for it however, this often does not happen. Patients should be educated about medication regimens that, when taken at 9 PM or bedtime, remain in the system for 24 hours or longer. By reducing discomfort and increasing effectiveness through ideal dosing, patient negligence in adhering to treatment may be minimized.

### Minimize anticholinergic burden

Medications with significant anticholinergic effects should be avoided if at all possible. This is not only because they worsen cognition, but because they also cause other unpleasant and uncomfortable side effects such as blurry vision, dry mouth, urinary retention, and constipation [21]. A seminal study demonstrated add-on cumulative anticholinergic adverse effects when patients simultaneously take several medications with anticholinergic properties [22]. Elderly patients particularly risk worsening dementia and/or delirium. Many unintended side effects can be mitigated simply by avoiding unnecessary dosing. For example, benztropine may be used as needed during the daytime [23]; but because Extrapyramidal Symptoms (EPS) do not occur during sleep, the administration of benztropine at bedtime is unnecessary. In fact, long term use of benztropine may worsen cognitive impairments in schizophrenia [23]. The serum anticholinergic activity in 45 participants with schizophrenia was significantly associated with impaired performance in cognitive tests [24]. The anticholinergic activity of benztropine 6 mg/day was five-fold higher compared to trihexyphenidyl 10 mg/day. Amantadine had no anticholinergic activity [25]. Anticholinergic medications may reduce the effectiveness of antipsychotic medications [26]. Decisions regarding the administration of antipsychotics with significant anticholinergic activity, such as clozapine and olanzapine, should also consider this risk [27].

## Suicide

In a study that identified 2,100 suicide deaths and 8,641 attempted suicides from 1996 to 2009 [28], individuals with schizophrenia, depression, SUDs and anxiety disorders were found to be at higher suicide risk shortly after receiving their diagnosis. In a meta-analysis of 44 studies with 50,004 subjects with bipolar disorder, women, younger age at onset of illness, depressive polarity of first illness episode, depressive polarity of current or most recent episode, comorbid anxiety disorder, any comorbid SUD, comorbid cluster B/borderline personality disorder and having a first-degree family history of suicide were significantly associated with suicide attempts. Suicide deaths, in general, were significantly associated with males and first-degree family history of suicide [29]. Hence, we can infer that with each comorbid diagnosis, the suicide risk increases. PHQ-9 item on suicide is a robust predictor of subsequent suicide attempts or completed suicide [30]. Thus, using the aforementioned studies and tools, clinicians must aim to identify high risk populations and stratify their individual risks to prevent suicides in these patients. Studies suggest that at least two medications, lithium and clozapine, might be effective in reducing suicidal behavior. However, since both are associated with substantial adverse effects and risks, neither can be given with impunity. In a systematic review of 32 RCTs in patients with unipolar depression, bipolar disorder, schizoaffective disorder, dysthymia, and rapid cycling, 1,389 patients received lithium and

2,069 received other medications. Patients who received lithium had fewer suicide deaths compared to other medications [31]. In a 44-year prospective study with 406 patients with mood disorders, lithium was found to significantly reduce suicide [32]. There is evidence to suggest that clozapine may be effective for suicide prevention in people with schizophrenia [33,34]. The European Psychiatric Association already recommends lithium in unipolar and bipolar depression, and clozapine in schizophrenia, for suicide prevention [35]. Hence, lithium and clozapine may be utilized more often in clinical practice to prevent suicide.

## Specific Disorders

### Dementia

With regards to Alzheimer's dementia, several RCTs of combination treatment with Acetylcholinesterase Inhibitor (AChEI) and the N-Methyl-D-Aspartate (NMDA) receptor antagonist, memantine, showed slowing of cognitive decline and improvement in cognition compared to AChEI monotherapy [36,37]. Functioning improved significantly in the Activities of Daily Living (ADL) [36]. At the end of year four, an effect size of 0.49 and 0.73, for cognition and ADL respectively, were shown for combination treatment versus monotherapy [37]. Clinically significant effect sizes of 0.2-0.4 were shown in all efficacy domains, such as cognition, functioning, and global outcome [38]. In data pooled from four 6-month RCTs, the donepezil-memantine combination (N=838) was clinically shown to be significantly better than monotherapy (N=570) in treating Alzheimer's dementia [39]. In 2014, the combination of donepezil and memantine (Namzaric [one pill]) was approved by the FDA for the treatment of Alzheimer's dementia. The Multi-Target Directed Ligand (MTDL) of galantamine and memantine has also been shown to be potentially useful in Alzheimer's dementia [40]. Galantamine is not only an AChEI, but also a positive allosteric modulator of the α4β2 and α7 nicotinic receptors. The galantamine-memantine combination (N=53) was significantly better for cognition than donepezil-memantine combination (N=61) in Alzheimer's dementia patients [41].

Benzodiazepines are widely used to prevent behavioral disturbances in the elderly population; this may worsen dementia and delirium [42] and is associated with significant fall risk. In 421 outpatients with Alzheimer's dementia with psychosis, aggression or agitation, participants were randomly assigned to treatment with olanzapine, quetiapine, risperidone, citalopram, or placebo for nine months. No differences were found between the medications and placebo [43-44]. Hence, in addition to judicious use of antipsychotics, acutely acting mood stabilizers, such as valproic acid, or other medications, such as propranolol or gabapentin, may be considered in treating agitation in dementia.

### Psychotic disorders

**Better utilization of medications and programs:** It is quite unfortunate that there has not been anything novel in the development of antipsychotics since 1952, when chlorpromazine first came into use. D2 antagonists are still a mainstay in the treatment of psychotic disorders. Clozapine has been very promising, and has been more effective than other antipsychotics in many cases. Even still, it remains underutilized [45]. People with schizophrenia have poor insight into their illness, which leads to nonadherence to treatment. More patients should be offered Long Acting Injectable (LAI) antipsychotics [46,47]. Those currently receiving them may also need reminders to receive the LAI. It is not uncommon for patients with psychiatric diagnoses to miss psychiatric follow ups. The assertive community treatment team, case managers, and treatment guardians should monitor adherence with medications and regular follow ups. This may be successfully executed by regular checking, visiting, and phone calls. Forty five out of the 50 states in the US have outpatient civil commitment laws. This may significantly improve medication adherence and regular follow ups.

**First generation antipsychotics versus second generation antipsychotics:** For several psychotic disorders, two to three antipsychotics are prescribed for one patient. Evidence, however, is lacking that more than one antipsychotic is more effective than one antipsychotic alone. Clinicians continue to use haloperidol per oral tablets 50-60 mg daily along with risperidone per oral tablets 16 mg daily - this is unacceptable. Because of severe EPS associated with high doses like this, patients are likely to discontinue these medications without discussing with their doctors. D2 receptor blockade above a 60% threshold is redundant.

When choosing an antipsychotic, it is also important to mitigate the potential for adverse long term residual effects. With the SGAs in use since the 1990s, we can infer that the Tardive Dyskinesia (TD), caused by the SGAs, is less when compared to the First Generation Antipsychotics [FGA] [48-50]. There is a growing body of evidence that suggests a ban on the use of haloperidol for its clearly neurotoxic effects [51]. On the other hand, SGAs promote neurogenesis [52,53]. Neurotoxicity from FGAs would be expected to be more problematic with chronic treatment. In a meta-analysis of 18 studies with 1,155 participants with schizophrenia, more progressive gray matter volume was seen in patients treated with at least one FGA, compared to those treated with only SGAs [54]. FGAs and SGAs may have different neurobiological effects [55]; yet they have similar clinical effectiveness, as shown in the CATIE study [56]. Given this information, some clinicians incorrectly believe that the use of FGAs with benztropine may be comparable to SGAs. The focus of the CATIE study was not to differentiate the neuroprotective effects between FGAs and SGAs [55]. Clinicians continue to believe that the FGAs have more antipsychotic effect than the SGAs which is not correct.

**Managing agitation in psychotic patients:** Agitation, physical aggression, and other symptoms are often managed by multiple antipsychotics. Considering agitation, which by definition is severe anxiety with restlessness, mischaracterization may be the cause of the inappropriate prescription. Clinicians often use agitation to characterize physical and/or verbal aggression, anger, irritability and pacing. These symptoms, however, can be effectively managed with mood stabilizers, propranolol, anxiolytics and effective management of related issues, such as insomnia, anxiety and withdrawal from substances. Instead, currently, patients are prescribed high doses of up to three antipsychotics including 1-2 FGAs. When the patient is irritable, physically aggressive, or showing warning signals like pacing, more antipsychotic per oral tablet or Intramuscular (IM) injection as prn is added. This is especially common in state hospitals and inpatients units. As mentioned earlier, this has not been shown to be effective. Rather, it has been shown that there is a higher risk for neuroleptic malignant syndrome, dystonia, akathisia and anticholinergic side effects with this practice. For simple sedative effects, diphenhydramine and/or benzodiazepine per oral tablet or Intramuscular (IM) injections may be more appropriate.

Thus, antipsychotic per oral tablet prn should be reserved for the indication of severe agitation. For anxiety and restlessness, hydroxyzine, benzodiazepines (not in people with the potential

for abuse), metoprolol, or propranolol prn [57] should be used more often. In the Emergency Room (ER) and within the inpatient unit, the antiquated practice of using IM injections of haloperidol, lorazepam and diphenhydramine together continues. Within this regimen, lorazepam may not be always necessary, and IM haloperidol is commonly associated with dystonia. Patients receiving IM haloperidol and diphenhydramine in the ER have reported acute dystonia after many hours. This may be because of the longer half life of haloperidol compared to diphenhydramine (nine hours in adults). This practice can and should be avoided. SGA IMs, with or without IM diphenhydramine, may be equally effective for the management of physical aggression. It is also a common practice to combine olanzapine IM and benzodiazepine IM within the ER and inpatient setting. Clinicians should be aware that concurrent use of olanzapine and parenteral benzodiazepines may result in potentiation of excessive sedation and cardiorespiratory depression [58] and Micromedex).

**Instructing patients on how to take antipsychotic medications:** It is unfortunate that many clinicians do not educate patients adequately on how to take their medications. For example, patients on ziprasidone and lurasidone, seldom know that they need to take these medications with 500 and 350 calories respectively. This increases bioavailability by 50% (package insert). Many hospitals have started addressing the issue, in the inpatient setting, by having a default order about calories associated with the medications. The nurse administering these medications ensures the necessary calories. This practice should be translated to the outpatient practice as well. Simply educating the patient that medications need to be taken with food is inadequate. They may often take it with food or snack items like yogurt, which may not provide the necessary calories needed to obtain the maximum bioavailability of the drug. It may be more appropriate to prescribe ziprasidone and lurasidone to be taken with dinner. Checking with patients and reminding them about taking these medications with necessary calories is essential.

**Managing extrapyramidal symptoms:** EPS, including akathisia, are daytime (while awake) symptoms. Hence, propranolol or benzodiazepines used to treat it may not be necessary late evening or at bedtime. Clinicians continue to use low dose benzodiazepines to manage catatonia. Dose equivalence of lorazepam 8-24 mg in divided doses daily is recommended [59]. Similarly, the first line to treat akathisia is beta blockers and second line benzodiazepines. Although it is often managed with benztropine, the evidence is not compelling to treat akathisia with it. Clinicians continue to prescribe benztropine IM to treat acute dystonia, even though IM diphenhydramine may be as effective and cost effective. The cost of diphenhydramine is $20.49/25 vials (50mg/1ml inj), whereas benztropine costs $159.34/5 ampules (2 mg/2ml inj). Using benztropine for Clozapine Induced Sialorrhea (CIS) is also not indicated, as it may add to the anticholinergic side effects of clozapine. Atropine eye drops are sometimes used sublingually to treat CIS. Glycopyrrolate 1 mg thrice daily, has been found to be effective for CIS [60,61].

**Metabolic parameters monitoring:** Clinicians should pay attention to the triglyceride/high density lipoprotein ratio. If it is ≥3.0, it is suggestive of insulin resistance [62]. In such cases, antipsychotics with weight gain liability should be avoided. In a meta-analysis of 307 studies, all antipsychotics, with the exception of ziprasidone, aripiprazole and amisulpiride, resulted in weight gain. Weight gain was more significant in antipsychotic-naïve patients [63]. Amisulpride is unavailable in the US, however, ziprasidone, aripiprazole and lurasidone may be used in people with BMI greater than 25 (FGAs may be considered keeping in mind the TD risk and neurotoxicity). It is a good practice to measure waist circumference routinely. In the US, 42% of people with schizophrenia have a BMI of ≥27. This places them at significant risk for insulin resistance and cardiovascular disease [64]. Therapeutic Life style Changes (TLC), including healthy diet and exercise, should be advised each visit. The FDA approved combination of bupropion-naltrexone, or topiramate may be tried in patients who, either do not follow TLC, or finds it only partially or totally ineffective.

Low Peripheral Arterial Compliance (PAC) is associated with stroke and cardiovascular events, such as atherosclerosis, stroke, and myocardial infarction [65]. Studies show quetiapine and risperidone use, as well as psychiatric diagnoses, are associated with low PAC [66]. Hence, quetiapine should be reserved for schizophrenia and bipolar diagnoses, and not used simply for insomnia. Secondary analyses with this data set showed that the low weight gain liability antipsychotics, such as typicals, ziprasidone, and aripiprazole have higher PAC when compared to high weight gain liability antipsychotics. Furthermore, not being on an antipsychotic has the highest compliance values, compared to high and low weight gain liability antipsychotics.

**Dosing schedules:** Clinicians prescribe haloperidol 2 mg four times daily; quetiapine 100 mg three times daily, and 400 mg at bedtime; risperidone 2 mg three times daily; and aripiprazole 10 mg AM and 5 mg bedtime. Based on the half-life, it is redundant to do this. Furthermore, it will lead to daytime sedation, and often prompt the patients to discontinue use on their own. All the above mentioned medications, except aripiprazole, can be given one time at bedtime. Daytime antipsychotic use may prompt benztropine or trihexyphenidyl use. The ramifications of its use as well as the risks of bedtime dosing have been described elsewhere.

## Bipolar Depression (BD)

The challenge of managing bipolar disorder remains in the depressive phase in which the patients present 80% of the time. Clinicians continue to use antidepressants in the treatment of BD, although evidence supporting its use is weak. The large NIMH funded Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial found that antidepressants were not superior to placebo in treating BD [67,68]. The FDA approved medications for the treatment of BD are quetiapine, lurasidone, lamotrigine, and olanzapine-fluoxetine combination. Although quetiapine has the most evidence, lurasidone, a relatively newer medication for BD, has better metabolic parameter profile compared to quetiapine. BD may be best treated by quetiapine, lurasidone, cariprazine [69], lamotrigine, or lithium. In treatment resistant cases, two, or rarely three, of the drugs can be used concurrently (quetiapine or lurasidone with lamotrgine and/or lithium). Lithium may not be effective for acute BD. Alternatively, valproic acid, carbamazepine, or oxcarbamazepine can be combined with quetiapine, lurasidone, lamotrigine, and/or lithium to treat BD [17,18,70-73]. Hence, when BD is foreseen in a patient presenting with mania, it may be appropriate to start them on 1-2 medications from quetiapine, lurasidone, lamotrigine and lithium. However, quetiapine and lurasidone may not be combined. There is evidence that pramipexole [74,75] and modafinil [76] are effective for BD. Four RCTs were suggestive that modafinil was beneficial for BD and MDD [77].

Although not commonly used in clinical practice, the olanzapine-fluoxetine combination for the treatment of BD was

studied and published by Eli Lilly and company investigators [78]. It should be noted that both olanzapine and fluoxetine are Eli Lilly and company products. In this study, olanzapine was found to be effective for BD as monotherapy; the olanzapine-fluoxetine combination was found to be significantly better than olanzapine alone. In this study, however, out of 833 subjects, only 86 were on the olanzapine-fluoxetine combination; the small sample is a limitation in drawing a firm conclusion. Unlike quetiapine and lurasidone, olanzapine is not currently FDA approved as monotherapy for BD. The olanzapine-fluoxetine regimen is one of the reasons why clinicians continue to justify the use of antidepressants in the treatment of BD. Another commonly used treatment for BD is valproic acid or carbamazepine with a Selective Serotonin Reuptake Inhibitor (SSRI) or a Serotonin Norepinephrine Reuptake Inhibitor (SNRI). Since neither class of medications has been shown to treat BD, the efficacy of these combinations to do so is unknown. Although some review papers argue that antidepressants may be effective, recent RCTs do not support the use of antidepressants in BD. No model currently exits to allow clinicians to predict which cases will respond to antidepressant treatment in BD. Even still, clinicians are too often starting patients on trials of antidepressants to treat BD before exhausting all the proven and approved medications available for effective BD treatment. In the STEP-BD study, mentioned earlier, paroxetine 30 mg or bupropion 300 mg were used daily. The use of any higher doses of these antidepressants or other antidepressants may lead to mood cycling. To counteract this, clinicians often increase the dose of the mood stabilizers. This ultimately leads to even more side effects, drug-drug interactions and cost. This reiterates why clinicians should be more inclined to use those proven and effective medications for BD discussed previously.

A clinical pearl in BD pharmacotherapy: quetiapine, lurasidone, lithium, and lamotrigine as monotherapy or as combination treatment are the mainstay. In bipolar I with psychosis, quetiapine and lurasidone are the drugs of choice. This is because it can treat both bipolar symptoms including BD and psychosis. Alternatively, a mood stabilizer and an antipsychotic may be started. But the antipsychotic is rarely stopped after psychosis remits.

### Laboratory testing

The blood draw for lithium level should be 10-12 hours after the last dose. This is commonly overlooked. Patients are unaware of this due to a lack of proper education about this. If the blood was not drawn within the narrow window of 10-12 hours, it is likely to be a falsely positive or falsely negative value. Likewise, the blood draw for divalproex should be 18 hours after the last dose. This is usually done after 12 hours.

## Major Depressive Disorder

It is important to treat patients according to dimensions indicated from PHQ-9. For example, the treatment of psychomotor retardation, anergia, anhedonia, and amotivation require dopaminergic medications. It must be noted however, that treatment for comorbid anxiety and insomnia are different. Unlike preferring FGAs over SGAs, clinicians are reluctant to go beyond SSRIs and SNRIs in the treatment of depression and use Tricyclic Antidepressants (TCAs) Monoamine Oxidase Inhibitors (MAOIs) [79]. TCAs [18] and Monoamine Oxidase Inhibitors (MAOIs) are underutilized [80,81]. Selegiline patch without dietary restriction is currently recommended when patients have Treatment Resistant Depression (TRD) stage III [79], and if they have anxious and atypical depression [81]. In a few patients, multiple dopaminergic medications, including stimulants, may be needed to treat TRD [20]. Medications like pramipexole (effect size 0.6-1.1) to target dopamine associated symptoms [18,75]; omega 3 fatty acids [82]; during pregnancy and breastfeeding [83]; and modafinil to target dopamine associated symptoms [84] are underutilized. Similarly, buspirone in anxious depression and liothyronine (T3 thyroid hormone) are underutilized in clinical practice as augmenting agents and as an adjuvant. This is despite evidence from the large Sequenced Treatment Alternatives to Relieve Depression (STAR-D) data. In an RCT, 75 patients with body mass index ≥30 kg/m$^2$, high concentrations of high-sensitivity C-reactive protein, low S-adenosylmethionine/S-adenosylhomocysteine ratio, and genetic markers at baseline were treated with L-methylfolate. The results showed significant improvement in depression when on L-methylfolate 15 mg compared to placebo [85].

In psychotic depression, aripiprazole may be the antipsychotic of choice because it can treat both depression and psychosis. In TRD, Electroconvulsive Therapy (ECT) and aerobic exercise have been shown to increase brain-derived neurotrophic factor [86]. ECT may be reserved for catatonic patients, acutely suicidal patients, treatment resistant stage IV, which is resistance to MAOI [79], or treatment resistant psychotic depression. ECT may worsen cognitive impairments associated with depression, and thus should be discussed with the patients. ECT-associated cognitive impairments and the potential role of the glutamatergic system have been suggested. Memantine 5-20 mg, administered daily before ECT, has been shown to improve cognitive performance after ECT [87,88]. In many facilities, maintenance ECT, to prevent relapse, is not done [89]. The Consortium for Research in ECT (CORE) reviewed 19 studies from 1997 to 2011. In these studies, successful ECT was followed by placebo, nortriptyline alone, or a combination of lithium and nortriptyline. It was found that continuation ECT was an effective alternative to continuation treatment with lithium and nortriptyline [90].

Patients may often be reluctant to discuss the sexual side effects of their medications. However, such side effects may play a part in the adherence to the medication. Clinicians should routinely check for this, and manage appropriately; to ensure that sexual side effects do not prompt nonadherence with treatment. The antidepressant with the least sexual side effect is bupropion. As discussed earlier with clinical use of antidepressants in the treatment of BD, medications like lamotrigine, quetiapine, and lurasidone are also being used as adjuncts in the management of MDD. Similarly, there is no supporting evidence in this case either. This practice may be extrapolation of the fact that aripiprazole is indicated for the treatment of MDD. In the treatment of MDD, clinicians may follow evidence based treatment including SSRIs, SNRIs, and TCAs. Medications mentioned earlier should be used as an adjuvant and to augment treatment. Medications such as omega-3 fatty acids, pramipexole and modafinil are effective for both MDD and BD. "For the present time, until a savior has arrived, one should fully use the weapons we have in our battle with depression [80]".

## Anxiety

The importance of identifying anxiety as a comorbidity or symptom versus a primary diagnosis was discussed previously with mood disorders. Often, the focus is on anxiety as a cross-cutting symptom. It is also extremely important to manage anxiety and comorbid anxiety. Clinicians may write prescriptions like buspirone

20 mg 9 AM and 9 PM for anxiety. Likewise, they may also write clonazepam 1 mg 9 AM, 1 PM, and 9 PM or at bedtime. Gabapentin can also be prescribed as 300 mg 9 AM, 1 PM and 9 PM; at bedtime; or four times daily. To target anxiety as a daytime symptom, 9 PM dosage is redundant. The half-life of buspirone and gabapentin are 2-3 hours and 5-6 hours respectively and thus, may be prescribed 2-3 times during the day. Bedtime dosing should be reserved for medications such as hypnotics. Nocturnal anxiety and nocturnal panic attacks may have to be treated with an anxiolytic with a long half-life. Anxiety is a common comorbid symptom associated with several psychiatric diagnoses. In a large study, (N=108,664) depression was associated with suicidal ideation, but anxiety led to suicidal behavior [91]. In the STAR-D study (N=1,450), subjects with anxious depression had a poorer prognosis [92]. Hence, proper detection, classification, and treatment of anxiety are critical.

## Posttraumatic Stress Disorder (PTSD)

Clinical use of prazosin in PTSD treatment is a major discovery in psychiatry in the last decade [93,94]. However, it is underutilized by many psychiatrists who do not recognize its effectiveness. Even when prescribing, an inadequately low dose at bed time is used. A higher dose (16-25 mg) and 2-3 divided doses may be needed to target daytime symptoms as well. Rarely, prazosin 30-45 mg daily may be needed [18]. Some hospitals have guidelines not to exceed prazosin 20 mg daily. Some patients may benefit with a dose higher than prazosin 20 mg and rigid hospital rules and policies have to be addressed on a case by case basis. Because both are α-1 blockers, one has to be cautious while combining prazosin and trazodone. There is potential for additive hypotension, as well as the possibility of priapism. Patients should be warned about this. If hypotension is a concern, it can be effectively managed with sodium chloride tablet 1-12 grams a day and/or fludrocortisone 0.1-0.4 mg daily [95]. Hypotension and/or having hypotensive symptoms are not, in itself, adequate reasons to not use prazosin in PTSD treatment. Apart from the dizziness, edema and palpitations are also common side effects of prazosin. Pedal edema can be effectively managed with a diuretic. If patients cannot tolerate prazosin, or if adherence to 2-3 times a day is an issue, doxazosin 4-8 mg (maximum dose 16 mg) once a day may be used [96-99]. In contrast to the short half-life of prazosin (2-3 hours), doxazosin has a half-life of 16-30 hours (average 22 hours). An added advantage is that the Gastrointestinal Therapeutic System (GITS) tablet of doxazosin can be started at 4 mg instead of 1 mg.

When treating PTSD, benzodiazepines can worsen nightmares and should be avoided [100]. There are several failed trials of SSRIs for PTSD. SNRIs, because of the norepinephrine effect, may offer a better alternative. However, whether the alpha-1 adrenoreceptor antagonist effects would be counteracted by the noradrenergic reuptake inhibitor action of SNRIs has not been empirically studied yet.

In a large phase 3 RCT at 17 Veterans Affairs Medical Center sites (N=304), prazosin was not significantly better than placebo to treat PTSD. Several case reports, review papers, open label trials, and RCTs with smaller sample sizes have showed prazosin in PTSD with good effectiveness signal. Thus, the lack of level 1 evidence should not exclude this treatment from consideration within the standard of care. In many cases, level 2 evidence, as shown in figure 1, may be sufficient for extrapolation into clinical practice. Extrapolating level 2 evidence in to clinical practice is not limited to PTSD and may be considered for other disorders and target symptoms.

## Alcohol and Substance Use Disorders in General Psychiatric Practice

Substantial numbers of patients with SUD and co-occurring psychiatric disorders are seen by general psychiatrists. Clinicians need to be cautious while prescribing benzodiazepines, stimulants, zolpidem, narcotic pain pills, or any other medications with abuse liability. Many centers do not administer withdrawal protocols for alcohol, benzodiazepines or opiates correctly, due to the lack of expert staff. Clinical Opiate Withdrawal Scale (COWS) and the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) are minimally utilized in major addiction units. Because withdrawal symptoms are not captured, patients withdrawing from alcohol, benzodiazepines, or opiates do not receive the necessary medications, such as buprenorphine, chlordiazepoxide, and benzodiazepines, for detoxification in a timely manner. Substance withdrawal is associated with exacerbation of PTSD symptoms as well as substance use relapse [101]. Hence, active control of withdrawal from substance and PTSD-related arousal symptoms should be concurrently addressed during detoxification of people with PTSD and SUD [101]. Failure to address PTSD in patients with SUD is likely to lead to relapse.

Buprenorphine has been shown to be as effective as buprenorphine/naloxone for the treatment of opiate withdrawal and opioid use disorder maintenance treatment. However, in the outpatient setting, it is difficult for many patients to find buprenorphine providers. The cost of 30 tablets of buprenorphine/naloxone 2/0.5 mg is $108.37, and buprenorphine/naloxone 8/2 mg is $200.62. On the other hand, buprenorphine 2 mg, costs $35.40 and buprenorphine 8 mg is $69.54/30. Clinicians should, again, take into account patient accessibility and cost while prescribing these medications. It is worth noting that, although the consensus is to avoid buprenorphine/naloxone in pregnancy, there is no evidence to suggest that buprenorphine is safer than buprenorphine/naloxone.

### Substance use disorders

In people with SUDs and attention deficit hyperactivity disorder, treatment with stimulants should be avoided. Rather, atomoxetine [102], bupropion or guanfacine should be considered. Varenicline, although effective for smoking cessation, carries an FDA black box warning for possible neuropsychiatric events, including depression, suicidal ideation, suicide attempt and completed suicide. Recently, the FDA has retained this warning. There is also an FDA warning for seizure with the concomitant use varenicline and alcohol. Although varenicline has a very long half-life (24 hours), all of the drug approval studies have shown that twice daily dosing yields optimal efficacy and tolerability. Many patients report nausea, insomnia, headache, and vivid dreams, and thus, cannot tolerate the recommended 1 mg twice dosing. Electronic cigarettes (E-cigarettes) are becoming more popular [103] as both an alternative and/or adjuvant to smoking cessation. Take-home emergency naloxone has been shown to prevent deaths from heroin overdose [104]. This practice is still in its infancy. Edentulism is common in patients on methadone. This can be due to poor oral hygiene, xerostomia (dry mouth syndrome [105], and/or the methadone sugar syrup [106]. Clinicians should coordinate with dental practitioners to address the oral health needs of methadone users to better ensure their general well-being [106].

### Alcohol use disorder

Unfortunately, for the treatment of AUD, there is only modest effectiveness with disulfiram, naltrexone and acamprosate. A meta-analysis of seven RCTs (N=1,125) with topiramate showed greater efficacy than naltrexone and acamprosate [107]. In general, topiramate, for the treatment of AUD, is underutilized. This is perhaps due to the slow titration needed and the central nervous system side effects. Several medications for AUD are in the level 2 evidence stage. A small RCT showed that prazosin may be effective for AUD [108]. A rodent study showed that the combination of naltrexone and prazosin was more effective in decreasing alcohol consumption than either drug alone [109]. This was corroborated by the first publication on this combination for AUD in humans [110]. There are large naltrexone and prazosin combination studies ongoing for the treatment of AUD.

Although not absolutely contraindicated, disulfiram should be used cautiously after gastric bypass surgery with banding and clips. Discussion with the gastroenterologist and/or bariatric surgeon and clear documentation are warranted, before starting disulfiram in patients with AUD and a history of gastric bypass surgery.

## Insomnia

Like anxiety, insomnia is a cross cutting symptom and is often associated with several psychiatric disorders. Using antipsychotics as a hypnotic is not a good clinical practice. The most commonly used antipsychotic for insomnia is quetiapine 25-200 mg at bedtime. The benefit of this medication in the treatment of insomnia has not been proven to outweigh its potential risks [111-116]. In 2010, 54% of the total quetiapine prescriptions in England were for the 25 mg tablet; 48% of the olanzapine prescriptions were 5 mg or lower; and 57% of risperidone prescriptions were for 1 mg or 500 mcg tablets [117]. There is no reason to use antipsychotics as hypnotics when several FDA approved medications for insomnia are available such as diphenhydramine, doxepin, ramelteon, zaleplon, zolpidem, and eszopiclone. Furthermore, benzodiazepines, such as temazepem, flurazepam and triazolam, as well as medications, like trazodone and mirtazapine 7.5-15 mg, are also commonly used as off-label in this regard.

## Conclusion and Future Directions

Psychiatric diagnostic systems need to be fully utilized, along with meticulous record keeping. Pragmatic practice today requires optimal use of the resources available (rather than saying "30 years of psychiatry, with no fundamental progress" Current Psychiatry, 2015). This may be done by translating novel treatments, with supporting level 2 evidence into practice. Evidence based approved practices should be utilized more often. Despite several pragmatic limitations, the practice of psychiatry can improve with continued medical education of new or revised criteria, emerging treatments and higher quality patient interactions. Clinicians should evaluate a case holistically, and use evidence-based medicine, practice guidelines, community standards of practice and incorporate off-label uses for medications appropriately. Clinicians should also receive the support from the mental health system to improve psychiatric practices within it. There are the recommendations on how to fix the troubled mental health system [118].

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