Editorial

13 COMMON ERRORS IN PSYCHOPHARMACOLOGY

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Though psychopharmacology is the most discussed aspect of Psychiatry in our academic programs, and we keep discussing it to the level of receptors and genetics in extensive details, the prescriptions in this part of the world are occasionally seen to contain repeated occurrences of certain erratic practices. This is a review of some common errors I get to see in the prescriptions - not only by psychiatrists, but also by neurologists, other specialists and medical officers - I come across during my clinical practice.

1. PROLONGED USE OF THP

Though no high quality evidence supports their efficacy in treating drug-induced Parkinsonism, anticholinergic agents like trihexyphenidyl (THP) enjoy a long history of expert recommendations and anecdotal success.[1] High use of anticholinergic drugs along with antipsychotics for long duration has been identified as an important issue in the treatment of schizophrenia in several countries.[2] Anticholinergics can cause a variety of distressing peripheral (e.g. dry mouth, urinary disturbances, and constipation) and central (e.g. cognitive impairment, worsening of tardive dyskinesia, and delirium) adverse effects, especially in the elderly.[2,3] In schizophrenia, they may worsen cognitive deficits[4] and psychosis,[5,6] and the patients may also abuse these agents.[7]

Current treatment guidelines for schizophrenia generally do not recommend long-term use of anticholinergics. For example, in the 2012 update[8] of its 1990 consensus statement[9] on prophylactic use of anticholinergics in patients on long-term neuroleptic treatment, World Health Organization (WHO) recommends that such agents should not be routinely used for prevention of extrapyramidal symptoms (EPS) in individuals on antipsychotics. According to a review from 2012, in schizophrenia patients, discontinuation of anticholinergics results in improvements in tardive dyskinesia, cognition and even other symptoms of the illness, and the authors recommended that clinicians should consider a gradual withdrawal of anticholinergics in stable patients receiving antipsychotics.[10] The Comprehensive Textbook of Psychiatry even points out that many schizophrenia patients given typical antipsychotics do not develop parkinsonism and hence do not need anticholinergics, and suggests that even their short term prophylactic use should be done on a case to case basis and restricted to patients with high risk of developing dystonic reactions.[11]

2. LEVODOPA FOR DRUG-INDUCED EPS

When a patient on an antipsychotic develops EPS, considering the nature of the symptoms, like tremors and rigidity, the patient or family often decides to consult another specialist, and gets a prescription for levodopa-carbidopa combination, probably since the prescribing specialist misses the history of antipsychotic exposure. Researchers from other parts of the world too have reported that dopaminergic agents are frequently and inappropriately prescribed to patients with drug-induced parkinsonism.[12]

Though dopaminergic agents like levodopa alleviate motor symptoms of Parkinson's disease, they are generally ineffective in drug-induced parkinsonism probably due to the antipsychotic blockade of D2 receptors.[1] In one report, even high-dose levodopa was not helpful in alleviating drug-

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induced parkinsonism.[13] Furthermore, dopaminergic agents may also exacerbate psychosis.

3. FEAR TO USE CLOZAPINE

Clozapine is an irreplaceable drug in psychiatry, with elective indications in treatment-resistant schizophrenia, suicide risk in schizophrenia spectrum disorders, aggressiveness or violence in psychiatric patients, psychosis in Parkinson's disease, and prevention and treatment of tardive dyskinesia.[14] However, it is being underutilized, probably due to uneasiness on the part of clinicians in managing adverse effects, particularly agranulocytosis, and a reluctance by patients to submit to frequent blood sampling.[15]

According to a review from 2014, the cumulative incidence of clozapine-induced neutropenia and agranulocytosis is only 0.8% over 15 months, and the most frequent period of occurrence is first 6-18 weeks of treatment.[14] Besides, the blood monitoring system has been effective in reducing both the incidence of clozapine-related agranulocytosis and the associated mortality rate.[15] Moreover, an Australian study reported that, during 2006-2010, even without any monitoring system, the maximum annual incidence of agranulocytosis caused by clozapine in the country would have been only 0.26%.[16]

Many experienced Indian practitioners believe that the rate of agranulocytosis is lower in our population than is reported in western literature. However, a 2010 review of Indian research on clozapine did not list any study that specifically assessed the incidence of agranulocytosis.[17] The study by Chand et al. on efficacy of clozapine in treatment resistant schizophrenia did not detect agranulocytosis in any of their subjects.[18] Another small, retrospective study (n=28) which primarily assessed thrombocytopenia in clozapine-treated patients did not find any instances of leukopenia, neutropenia, or agranulocytosis.[19]

If the costs and efforts involved in prolonged blood monitoring is a concern, a 2006 review, which assessed if the blood monitoring can be discontinued after six months, found that the chance of clozapine-induced leukopenia or agranulocytosis decreases exponentially over time, and concluded that after at least six months of treatment with clozapine, the mortality involved in stopping white blood cell monitoring is about the same as the mortality associated with other medications such as mianserin or phenylbutazone and with life in general (traffic or occupational accident), and recommends that if the patient has been well informed and wishes to stop the monitoring, it is a medically justifiable option to do so.[20] Another review points out that there have been only five reports of neutropenia or agranulocytosis that happened after more than six years of treatment with clozapine.[14]

4. USE OF THIORIDAZINE

Thioridazine, the good old antipsychotic, is making a resurgence in various other specialties as an effective treatment for multidrug resistant tuberculosis[21] and various cancers.[22,23] However, its continued use as an antipsychotic, as still practiced by at least some psychiatrists, neurologists, etc., may be unscientific and harmful to the patients, considering its high cardiotoxicity. A recent metaanalysis on sudden cardiac and sudden unexpected deaths related to antipsychotics concluded that, of the nine antipsychotics investigated, thioridazine had the biggest odds ratio (OR=4.58, 2.09-10.05).[24] Another review reported that, among antipsychotics, thioridazine remains the agent most associated with QTc prolongation.[25] Regulatory bodies in Australia, North America and United Kingdom have even placed restrictions on its prescription.[26] A review recommends that new patients should not receive this agent, but adds that existing patients benefiting from modest doses should not be denied it unless clear-cut risk factors for cardiotoxicity are evident.[26]

5. FLUPENTHIXOL FOR ANXIETY

Flupenthixol-melitracen combination was one of the most common prescriptions for depression and anxiety in the country before it got banned in 2013. The health ministry cited two reasons for the ban —

(i) Melitracen is reported to be not efficacious as a single agent in depression. (ii) Flupenthixol is associated with potentially serious neurologic side effects.[27]

Now, flupenthixol alone and in combination with other antidepressants are being promoted as alternatives to the banned combination. However, research supports the health ministry's stand on adverse effects of flupenthixol. For example, a case control study of patients with anxiety or depressive disorders compared patients treated with flupenthixol in a "low, non-antipsychotic dosage" (n=106) to otherwise comparable patients who had never been treated with neuroleptics (n=37), and found tardive dyskinesia and EPS in 6.7% and 26% respectively of the flupenthixol group. The corresponding rates in the control group were 0% and 16% respectively.[28]

Is it only a question of adverse effects? What about efficacy? A 2006 review concluded that, except for trifluoperazine, there is no large, well-designed study of any other antipsychotic, including flupenthixol, in the treatment of primary or comorbid anxiety symptoms or disorders.[29]

6. PROPRANOLOL FOR ANXIETY

A recent systematic review and metaanalysis on the use of propranolol for treatment of anxiety disorders concluded that, at present, the quality of evidence for its efficacy is insufficient to support its routine use in the treatment of any anxiety disorder.[30]

7. SSRIS FOR PATIENTS ON ASPIRIN

Selective Serotonin Reuptake Inhibitors (SSRIs) lead to a modest increase in the risk of upper GI bleeding.[31] Mechanisms postulated include depletion of platelet serotonin and subsequent reduction in ability to form clots,[31] and increased gastric acid secretion and subsequent irritation to gastric mucosa.[32] Elderly and those with a history of GI bleeding are at the greatest risk,[31] and the risk may be greatest with SSRIs that have a high affinity for serotonin transporters.[33] Gastroprotective drugs like the proton pump inhibitors may substantially reduce this risk, but do not completely eliminate it.[31] Co-prescription of low-dose aspirin at least doubles the risk of GI bleeding associated with SSRIs alone.[34]

Which antidepressant would be safe for depressed patients with coronary heart disease (CHD) who are receiving aspirin? Though a thorough search of the literature did not reveal any specific guidelines in this regard, it seems mirtazapine would be a valid choice. According to a guideline endorsed by Royal College of General Practitioners, Royal College of Psychiatrists etc., mirtazapine is safe for use in CHD and can be used in situations where SSRIs are "ineffective or poorly tolerated".[35] A review from 2008 adds that mirtazapine appear to be safe to use after myocardial infarction and that it can reduce mortality.[36] On the other hand, venlafaxine is contraindicated in people at high risk of cardiac arrhythmias and may cause hypertension in higher doses, and caution is indicated when it is used in CHD and blood pressure monitoring is advised.[35] About bupropion, a recent systematic review detected a trend toward worse CHD outcomes after treatment with the agent.[37] Aerobic exercise has been shown to improve not only depression, but also cardiovascular health.[38]

8. UNDERUSE OF ECT

Systematic reviews and metaanalyses have concluded that electroconvulsive therapy (ECT) -

- Is significantly more effective than pharmacotherapy in management of depressive disorders,[39]
- In combination with antipsychotics, may be considered an option for people with schizophrenia, particularly when rapid global improvement and reduction of symptoms is desired or when there is limited response to medication alone,[40]
- Is effective in all forms of catatonia, even after pharmacotherapy with benzodiazepines has failed, with response rate ranging from 80% to 100%, and should be considered first-line

treatment in patients with malignant catatonia, neuroleptic malignant syndrome, delirious mania or severe catatonic excitement.[41]

However, though the contributions of Indian researchers to the field of ECT has been substantial,[42] off late its use has drastically decreased in this part of the world, even in the teaching institutions — to such an extent that, in the recently held Postgraduate Training Program of Indian Psychiatric Society South Zone, of which I was the Organizing Secretary, following the demand from teachers and students alike, we had to include a hands-on training session on ECT.

According to research from other countries, outdated and inaccurate depictions in films are a common source of knowledge on ECT for the general public,[43] considerable stigma that still surrounds ECT probably remains the greatest barrier to its public acceptance,[44] and education using videotapes has been shown to alter the attitudes toward ECT in nursing students[45], attorneys,[46] etc. However, and curiously, Indian studies have revealed quite satisfactory knowledge and positive attitude in patients and relatives,[47,48] and in a survey of Indian psychiatrists most respondents expressed positive feelings about ECT.[49]

The decline in use of ECT deserves in depth scrutiny by our researchers and suitable interventions by all concerned.

9. PHENYTOIN FOR ALCOHOL WITHDRAWAL SEIZURES

A metaanalysis of randomized, placebo-controlled trials on secondary prevention of alcohol withdrawal seizures (AWS) demonstrated that phenytoin is ineffective.[50] A 2009 update[51] of the 2005 guidelines of European Federation of Neurological Societies on management of alcohol - related seizures[52] recommend that benzodiazepines (BZDs) should be used for prevention of AWS recurrence (Level A recommendation), and that phenytoin is not recommended for this indication (Level A recommendation).

Physiological dependence to alcohol results from compensatory changes during prolonged alcohol exposure, including internalization of gamma-aminobutyric acid (GABA) A receptors, which allow adaptation to the immediate effects of alcohol. AWS are believed to reflect unmasking of these changes, and may also involve specific withdrawal-induced cellular events that confer reduced inhibitory function (rapid increases in α4 subunit–containing GABA A receptors, for example).[53] A possible explanation for the disparity in efficacy of phenytoin and BZDs in AWS is that, while phenytoin acts against sustained high frequency repetitive firing (SRF) of action potentials, BZDs, beside acting against SRF, also modify postsynaptic GABA responses.[54]

10. LONG TERM BZDS IN ADS

WHO guidelines on management of alcohol withdrawal specify that, in general, use of BZDs should be limited to the first 3 to 7 days after cessation of alcohol.[55] A systematic review from 2013 recommend that, if one is following the fixed dose regime, the BZD should be gradually tapered off over 7-10 days.[56]

The efficacy of BZDs for long-term treatment of alcoholism has been more controversial, and most reviews of drug treatment of alcoholism conclude that their routine use is not indicated on a long-term basis.[57] Controlled studies indicate that BZDs do not improve abstinence rates.[57] Such use also poses a risk of development of BZD abuse, especially in alcoholism patients with severe dependence or polydrug abuse.[58] However, the clinical reality is that many patients of alcoholism are treated by BZDs during detoxification and then continue to receive them for treatment of insomnia or anxiety disorders.[57]

What are the safer, efficacious alternatives to manage insomnia or anxiety disorders in this population? A 2011 systematic review of pharmacological treatment of insomnia in alcohol recovery concluded that the agent with most data supporting its efficacy is trazodone.[59] According to

a recent review, brief behavioral therapies have shown long-lasting benefit without worsening of drinking outcomes, and hence are the treatment of choice.[60] Limited, preliminary research has shown that acamprosate and topiramate, agents with some proven efficacy for relapse prevention in alcoholism, also have an additional sleep-promoting activity.[60]

A review of publications on management of comorbid anxiety and alcohol disorders concluded that alcohol-related and anxiety disorders should not be lumped together as one global condition, but as separate distinct combinations (for e.g. alcohol dependence and panic disorder, alcohol dependence and generalized anxiety disorder, etc.); and added that the recommended treatment approach, supported by the evidence, is to offer separate and parallel therapy for alcohol dependence and the anxiety disorder.[61] A recent Cochrane review of pharmacotherapy for anxiety and comorbid alcohol use disorders reported that the majority of data for efficacy and tolerability available are for SSRIs.[62]

11. CHLORDIAZEPOXIDE IN CIRRHOSIS

For management of alcohol withdrawal or other indications, long-acting BZDs like diazepam and chlordiazepoxide are better avoided in patients with hepatic impairment as there is a risk of precipitating hepatic encephalopathy through accumulation of CNS-depressing metabolites. Instead, in this context, it is better to use a short-acting BZD that has no active metabolites, such as lorazepam.[63]

12. FEAR TO USE DISULFIRAM

Disulfiram is one of the most effective pharmacological interventions for relapse prevention in alcohol dependence. A 2014 metaanalysis by Skinner et al., based on 22 studies, found disulfiram to have overall higher success rate than controls (Hedges' g = .58; 95%CI = .35–.82), and to be more effective than naltrexone (g = .77, 95%CI = .52–1.02) and acamprosate (g = .76, 95%CI = .04–1.48).[64] A 2004 review by Fuller and Gordis tried to answer the question "With the advent of newer medications which act directly on the biological processes influencing the addiction to alcohol, does a medication that acts indirectly to deter drinking have a role in contemporary alcoholism treatment?", and reached the following conclusion: "The answer is a qualified yes. Disulfiram does not have to be used when a patient presents initially for treatment. However, if the patient is struggling to achieve sobriety, the supervised administration of disulfiram is warranted".[65] Indian studies too have proven that disulfiram is superior to acamprosate,[66] naltrexone[67] and topiramate.[68] A naturalistic, uncontrolled one-year follow up study of 60 cases of alcohol dependence in JIPMER, Pondicherry, found that duration of disulfiram use was strongly associated with a favorable outcome.[69]

Still, many psychiatrists are reluctant to use the agent, especially due to fear of fatal disulfiram-ethanol reactions (DER).

A review from 1999 concluded that deaths from DER have not been reported in recent years, possibly because the dosages used are lower than those used 40 years ago and patients with cardiac disease are now excluded from treatment.[70] About the overall safety of disulfiram, the review commented that it can be viewed as a drug with a moderate record of adverse effects, while alcohol dependence is associated with a high morbidity and mortality. Similarly, in another review, Brewer commented that compared with the toxicity of alcohol, the toxicity of disulfiram is trivial.[71] Skinner et al. had concluded that there was no difference between disulfiram group and control group in deaths or serious adverse events requiring hospitalization.[64] (However, the authors added a caution that their finding of safety of disulfiram may be attributed to the selection of subjects in RCTs, where the screening process is generally more rigorous than that used for clinical disulfiram use.) According the review by Fuller and Gordis, the side effects are usually minor, and serious adverse reactions are uncommon, although monitoring for hepatotoxicity should be done.[65] A 2013 review provides a list of safety precautions that should be

followed when disulfiram is prescribed, and concludes that when the safety recommendations are in place, the administration of disulfiram can be considered a safe practice and within an acceptable risk profile.[72]

13. SYLIMARIN FOR ALD

According to a 2007 Cochrane review, based on 13 RCTs that assessed sylimarin in 915 patients with alcoholic and/or hepatitis B or C virus liver diseases, sylimarin versus placebo or no intervention had no significant effect on mortality (RR 0.78, 95% CI0.53 to 1.15), complications of liver disease (RR 0.95, 95% CI 0.83 to 1.09), or liver histology.[73]

Then how does one manage alcoholic liver disease (ALD)? According to Korean Association for the Study of the Liver Clinical Practice Guidelines, alcohol abstinence is the single most important treatment for improving survival in alcoholic hepatitis, and steroids are needed for patients with severe alcoholic hepatitis who have an mDF score of ≥32.[74] Detailed recent guidelines on management of ALD are available also from European Association for the Study of the Liver[75] and American College of Gastroenterology.[76]

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