31st Annual Psychopharmacology Update: Response to Unanswered Questions

By David Osser, M.D., Program Chair

On Saturday, Nov. 21, 2020 the MPS held its 31st Annual Psychopharmacology Update Virtual conference via Zoom. There were many unanswered questions. The answers below are not guaranteed to be correct! If you see any errors, please let me know.

**What is the evidence that antipsychotics cause neurotoxicity and cortical brain volume loss?**

Answer: The evidence in schizophrenia is still somewhat under debate because it’s hard to tease out the effect of the underlying illness causing the same kind of problems, though there have been very concerning data in monkeys showing similar brain structural changes. However, a recent secondary analysis from the STOP-BD randomized placebo-controlled trial of olanzapine (and sertraline) in patients with psychotic depression found the same changes in brain structure from olanzapine in this non-schizophrenia population. (Voineskos AN et al. JAMA Psychiatry 2020;77(7):674-83. The authors conclude that this harm should be taken into consideration when you prescribe antipsychotics long-term for mood and anxiety disorders when there are alternative medications you could use.

**What medications can be used to assist with benzodiazepine tapering?**

Answer: According to a Cochrane review, none have good evidence. (Baandrup et al, 2018) However, the Mass. General group did studies decades ago of the “alprazolam to clonazepam” switch, and still recommended using this in their Handbook of Psychiatric Drug Therapy, 6th edition (Labbate et al, 2010).

According to this method, one adds clonazepam to the alprazolam in an equivalent dose on day one. So, if the patient is on 4 mg of alprazolam, that would be 2 mg of clonazepam (to be given 1 mg bid). Then, over the next week, the original dose of alprazolam is still permitted on an as-needed basis, but the patient is encouraged to gradually reduce the as-needed doses as the clonazepam (which has a 30–50-hour half-life) reaches steady state levels. If at the end of a week the patient still seems to need any alprazolam, they are not permitted to have any, but they should increase the clonazepam dose by 0.25 to 0.5 mg weekly until they become stable. Then, a slow taper of clonazepam can be considered to get off the benzodiazepine.

The often-cited 2002 “Ashton Manual” ([https://www.benzo.org.uk/manual/](https://www.benzo.org.uk/manual/)) recommendations differ. Dr. Ashton prefers to use diazepam rather than clonazepam for the switch. Reviewing it, I see that she does not mention the problem of rapid absorption and associated well-evidenced high abuse potential of diazepam (Griffith and Wolff. J Clin Psychopharmacol 1990; 10: 237-43), putting her faith in the long half-life of its metabolite desmethyldiazepam. Furthermore, she cites no studies of this switch strategy – it’s only her belief in it or experience with it. Here’s what she says about clonazepam:

“Some doctors in the US switch patients onto clonazepam, believing that it will be easier to withdraw from than say alprazolam or lorazepam because it is more slowly eliminated. However, clonazepam is far from ideal for this purpose. It is an extremely potent drug, is eliminated much faster than diazepam, and the smallest available tablet in the US is 0.5 mg (equivalent to 10 mg
It is difficult with this drug to achieve a smooth, slow fall in blood concentration, and there is some evidence that withdrawal is particularly difficult from high potency benzodiazepines, including clonazepam.” (but no evidence is cited)

But, as noted, clonazepam has evidence that it works. She “believes” it would be easier to withdraw from diazepam but that’s not the same as there being evidence of it. While it’s true that clonazepam’s half-life isn’t as long as desmethyldiazepam, it is pretty long and much longer than alprazolam and, as the evidence suggests, adequate for this purpose. In short it looks like this portion, at least, of the “Ashton Manual” is more eminence-based medicine rather than evidence based.

Are there pharmacodynamic differences between high and low potency benzodiazepines?

Answer: Not to my knowledge. But the pharmacokinetic differences are considerable and strongly affect choice. For example, as just noted, diazepam is highly lipid soluble and thus rapidly absorbed by the lipid membrane in the gut, and this rapid absorption gives a “buzz” acutely for some individuals which contributes to its abuse potential. Oxazepam, by contrast, is slowly absorbed because it is more water soluble, and can take 5 hours to reach peak concentration after a dose. It probably has little utility (beyond placebo effect) as an as-needed medication for a patient seeking a rapid effect.

For cardiac patients, such as post-MI, how cautious should you be with prazosin, clonidine, or propranolol for PTSD? Answer: Definitely consult with your patient’s PCP or cardiologist for assistance with this determination.

For OCD patients who have an unsatisfactory response to an SSRI, Mass. General prefers glutamatergic drugs. Answer: In our OCD algorithm, (Beaulieu AM et al. Psychiatry Research 2019; 281:112583) we propose that clinicians consider second-generation antipsychotics, glutamatergic agents (e.g., memantine, lamotrigine, n-acetylcysteine), or rTMS for augmentation. We did not express a preference. Clinicians can review these options with the patient and their side effects and evidence and make a collaborative decision.

Can you just switch citalopram to escitalopram and take advantage of the reduced effect on QTc and somewhat greater efficacy in the head-to-head comparisons? Answer: Probably you can. Keep in mind that the switch ratio is 4:1 according to the package inserts. So, 40 mg of citalopram equals 10 mg of escitalopram. It’s not 2:1 as you might think given that there are two enantiomers of equal concentration in citalopram. It has been speculated that r-citalopram may have an inhibiting effect on the effectiveness of s-citalopram when they are both present at the same time. But remember that if you exceed the package insert maximum dose of escitalopram of 20 mg and go to 30 mg, the QTc prolongation becomes quite significant.

Have any withdrawal problems been noted with bupropion? Answer: There have been no reports of this.

Would vaping have an effect on clozapine levels? Answer: No. It’s the hydrocarbons in cigarette smoke that induce clozapine metabolism, not the nicotine.
It wasn't clear how increasing clozapine levels with fluvoxamine would lower the risk of weight gain. Answer: Fluvoxamine blocks the metabolism of clozapine to norclozapine which is mediated by Cytochrome P450 1A2. Some research has suggested that the weight gain risk with clozapine comes primarily from norclozapine. Therefore, with fluvoxamine, you sharply raise the level of the parent compound and lower the norclozapine level and this could reduce weight gain risk. Constipation and other anticholinergic side effects might also be less with the parent compound. The two studies (Lu ML et al. J Clin Psychiatry 2004; Lu et al. Schizophrenia Research 2018) did not find any increase in psychosis from adding fluvoxamine. So, this is an interesting combination worthy of further study.

If you need to stop clozapine quickly due to neutropenia, how do you stop the cholinergic rebound and possible associated psychosis? Answer: Add an anticholinergic, such as benztropine, as soon as clozapine is stopped. Then slowly taper it off if clozapine is restarted or as the next antipsychotic is given. (Miodownik C et al. J Clin Psychiatry 2006; 67: 1204-8)

I use benztropine and Botox for sialorrhea from clozapine. What are you suggesting? Answer: The best evidence is with glycopyrrolate 1-4 mg bid and metoclopramide 10-30 mg daily. They have placebo-controlled trials. Sublingual atropine drops are also used and have evidence but we have no experience with it.