Treating ADHD in Prison: Focus on Alpha-2 Agonists (Clonidine and Guanfacine)

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Attention deficit/hyperactivity disorder (ADHD) is prevalent in prison populations, but optimal treatment recommendations in prison are uncertain. Stimulants are problematic because of the potential for abuse. This article is a review of medication options for ADHD, focusing on the α2 agonists clonidine and guanfacine, which, in their extended-release (ER) forms, are U.S. Food and Drug Administration (FDA) approved for the treatment of ADHD, although they are probably less efficacious, overall, than stimulants. Advantages of α2 agonists in prison include: they are not controlled substances and have no known abuse potential; they may be particularly helpful for ADHD with associated aggression and other features of conduct disorder; they may reduce anxiety and symptoms of posttraumatic stress disorder; and they are somewhat sedating. The pharmacology of these agents and the presumed mechanism of action are discussed, including the fact that guanfacine more specifically affects α2A receptors, which are postsynaptic in the frontal cortex. Other differences between clonidine and guanfacine and between the generic immediate-release (IR) forms and the ER forms are also discussed. The IR forms, while themselves not FDA approved for ADHD, may, with dosage adjustment, be reasonable alternatives (with considerable cost savings). Overall, given the FDA-accepted evidence of efficacy, the lack of abuse potential, and the favorable side effect profile, α agonists may be the treatment of choice for prison inmates with ADHD.

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A reasonably large percentage of prison inmates have, or have had, attention deficit/hyperactivity disorder (ADHD); estimates range from 9[1] to 45 percent.[2] The data are not surprising, given that studies indicate that a substantial subgroup of children with ADHD also have conduct disorder.[3] The symptoms of ADHD (and conduct disorder) persist into adulthood,[4,5] and some of these symptoms (certainly features of conduct disorder and possibly other symptoms of ADHD) increase the risk that these individuals will end up in prison as adults.[6] In childhood, in a school setting, difficulty concentrating and motor hyperactivity may be the most prominent symptoms; in prison, excitability and impulsivity, especially impulsive aggression, are likely to be the most problematic symptoms. Retz and Rösler,[7] in an excellent review, suggested that ADHD, in a forensic population in Germany, is specifically associated with impulsive (and affective) aggression (not with "instrumental" aggression, i.e., aggression intended to achieve a goal). It is unclear how best to treat inmates with ADHD; the lack of a treatment strategy is of particular concern for inmates who were receiving stimulants before prison, since prison inmates are generally entitled to treatment at the "community standard." This article is a brief review of medication prescribed for ADHD in prison, with a focus on α2 agonists.

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Medication for ADHD

Stimulants

The stimulant medications, which are so helpful for childhood ADHD, can also be helpful for adults with similar symptoms.[8] However, most prison in-

mates have a history of substance abuse,[9] making prescribing a stimulant in prison problematic. A protocol for prescribing stimulants in prison inmates was presented by Appelbaum.[10] That article and the commentary by Burns[11] discussed the complexity of prescribing stimulants in prison, including feigning of symptoms to obtain stimulants. Stimulants can be a valuable commodity in prison; inmates are known to abuse, hoard, and sell medicines much less "attractive" than stimulants (e.g., antidepressants and antipsychotics).[12]

Also, although stimulants are helpful for improving concentration and reducing motor hyperactivity in children, it is less clear that they are helpful for the symptoms likely to be most problematic in adult prison inmates (e.g., impulsive aggression). For example, Connor *et al.*[13] suggested in a review that patients with ADHD (<18 years old) with concomitant oppositional defiant disorder (i.e., with defiant and aggressive symptoms) do not respond as well to stimulants as do patients with ADHD alone. So the risks involved with prescribing stimulants in prison may generally outweigh the potential benefits.

Atomoxetine

Atomoxetine is a nonstimulant that has been found to be useful in treating ADHD in children and adults.[14] A comprehensive review by Garnock-Jones and Keating[15] suggests that it may not be as effective overall as sustained-release stimulants, but it is better than a placebo, and may be superior to stimulants in some aspects of quality of life (because of different side effects). Their review also suggested that atomoxetine is as effective for the impulsivity of ADHD as it is for the impaired concentration (and that atomoxetine may be particularly useful for patients with comorbid anxiety). However, in another review, Patel and Barzman[16] concluded that atomoxetine is better at improving concentration than at improving impulsivity, excitability, and aggressiveness. Polzer *et al.*,[17] presented data indicating that atomoxetine may actually increase irritability and aggression; but Pappadopulos *et al.*,[18] in a meta-analysis, found reduced aggressiveness in children with ADHD who were prescribed atomoxetine (although methylphenidate reduced aggression more). Bangs *et al.*[19] did not find that atomoxetine consistently reduced symptoms of oppositional defiant disorder (ODD), although it reduced ADHD symptoms.

Alpha-2 Agonists

The final category of medicines that have been approved and found to be helpful for ADHD is the α2 agonists, clonidine and guanfacine.

History

Clonidine has an interesting history. It (and other α2 agonists) stimulates inhibitory presynaptic norepinephrine receptors in the locus ceruleus, reducing norepinephrine activity; this was thought to explain its efficacy for its first approved use, to reduce blood pressure.[14] Because it reduces norepinephrine activity, it was reasonable to think that clonidine might be of benefit for anxiety disorders (given the role of norepinephrine in the fight-or-flight response), and some small studies found it to be of some benefit for anxiety (e.g., Hoehn-Saric *et al.*[20]), but approval for this indication was never pursued. Clonidine has also been used to reduce symptoms of opiate withdrawal (presumably the mechanism also involves its norepinephrine-reducing effect[21]). Clonidine and guanfacine may also be helpful for posttraumatic stress disorder (PTSD)[21–23] (which is a common comorbid diagnosis in prison[24]). Of note, use of α agonists for PTSD was tried partly because of the similarity of some symptoms of opiate withdrawal and PTSD.[21]

Immediate-Release Alpha-2 Agonists for ADHD

Clonidine was first used for ADHD (in the mid-1980s) because it had been used for tics and Tourette's syndrome. Some children with tics also have symptoms of ADHD, and it has been noted to be helpful for these symptoms. Several encouraging studies (mostly small and investigator initiated) reporting evidence of efficacy in children with ADHD (with and without Tourette's) were then conducted with clonidine[25] and later with guanfacine.[26] A 1999 review[27] of studies involving clonidine concluded that clonidine alone reduces the core symptoms of ADHD, but with a smaller treatment effect than that obtained with stimulants.

Interest in standard (now known as immediate-release (IR)) clonidine and guanfacine subsequently waned, apparently because of the loss of patent protection for these drugs. There was no financial incentive to conduct the large studies needed for U.S. Food and Drug Administration (FDA) approval (for a new indication: ADHD). The combination of stimulants and IR clonidine has also been studied

relatively little.[28,29] However, Palumbo *et al.*[30] conducted a study comparing clonidine, methylphenidate, the combination (both medications), and placebo in 122 children with ADHD. The results, consistent with those in the literature, showed that clonidine was somewhat beneficial, but was not as effective as methylphenidate.

Extended Release

Once extended-release (ER) forms of these drugs (with new patent protection) were developed, interest and funding revived. Both ER clonidine and ER guanfacine have been studied, have been found to be helpful for ADHD in children and adolescents, and are FDA approved for this indication. The available studies indicate benefit for all of the cardinal symptoms of ADHD, including impaired concentration, hyperactivity, excitability, and impulsivity (Hirota *et al.*[31]). The ER form of clonidine now has a generic equivalent, but the ER form of guanfacine still has patent protection.

Studies and reviews demonstrating the benefit of the ER forms of clonidine include Jain *et al.*,[32] who reported benefit from clonidine ER in pediatric patients with ADHD; Kollins *et al.*,[33] who reported that clonidine ER can be helpful if added to a stimulant for children and adolescents who have only a partial response to stimulants; and Croxtall.[34] Faraone *et al.*,[35] and Bukstein and Head[36] concisely reviewed the use of guanfacine ER for ADHD in children and adolescents, concluded that it too is useful. A recent meta-analysis[31] attempting to compare benefit from α2 agonists with other medication options (this type of meta-analysis, inherently, is of uncertain validity) reported overall evidence of benefit, comparable with atomoxetine, but not as much as with stimulants.

The studies of α2 agonists for ADHD, in both the IR and ER forms, have mainly been performed in children and adolescents. None is FDA approved for adults, but it is generally true that drugs found to be useful for children and adolescents, at least for psychiatric conditions (including ADHD), are also helpful for adults. So it is not unreasonable to think that studies in younger individuals are also relevant to adults.

Alpha-2 Agonists for ADHD With Aggressive and Oppositional Symptoms

Of particular relevance to a prison population, several researchers have looked specifically at the benefit from α2 agonists in patients with ADHD and concomitant aggressive and oppositional symptoms. Hazell and Stuart[37] reviewed several open-label studies and reported on a double-blind study involving 67 children (ages 6–14 years) taking stimulants for ADHD, who also were aggressive and had a concomitant diagnosis of either conduct disorder or ODD. Children were continued on stimulants and were randomized to clonidine or placebo. Results showed significant benefit from clonidine (compared with placebo) on ratings of conduct disorder symptoms. These were children, and all were receiving stimulants, but it suggests that clonidine would be particularly helpful in patients with ADHD and concomitant symptoms of conduct disorder or ODD. In a later review, Hazell[38] concluded that clonidine can alleviate the ODD component in combined ADHD/ODD, and the combination of a stimulant with an α2 agonist has been presented in several practice guidelines (e.g., American Academy of Child and Adolescent Psychiatry[39]). Patel and Barzman[16] reviewed the pharmacology of pediatric ADHD and associated aggression and indicated a need for future research, but also concluded that α2 agonists can reduce irritability and aggressiveness in children with ADHD. Hirota *et al.*[31] reached similar conclusions. The one large ($n = 217$) multicenter study of α2 agonists for ADHD with associated aggression (with ODD) was funded by Shire Pharmaceuticals (which produces ER guanfacine).[40] It reported ER guanfacine to be significantly better than placebo for overall ADHD symptoms and specifically better for oppositional symptoms in children (ages, 6–12 years) who had ADHD and oppositional symptoms (the children were not receiving concomitant stimulants).

Mechanism of Action: Alpha-2 Subtypes

Both clonidine and guanfacine are α2 agonists. Three α2 subtypes have now been identified[41]: 2A, 2B, and 2C. Guanfacine is more selective for the 2A subtype; clonidine binds equally to all three subtypes. Whether this is relevant to a benefit in ADHD is not altogether clear, as noted by Sallee *et al.*[42] in a review. Several papers (e.g., Arnsten[43]) focusing on the importance of the α2A receptor acknowledged support from Shire and reported the advantages of guanfacine (and the advantages of the ER form compared with the IR one).

Historically, when α2 receptors were considered to be primarily agonists of presynaptic receptors on norepinephrine (NE) neurons (inhibiting NE release), it was hard to understand why α agonists would help patients with ADHD, given that other medications for ADHD (e.g., stimulants) increase norepinephrine (and dopamine) activity. The discovery of postsynaptic α2A receptors in the prefrontal cortex[43] provided a better theoretical rationale for α2 agonist benefit in ADHD. A genetic study[44] reported an association between the gene for α2C receptors and ADHD. Despite the theories, it remains unclear how these medications work in alleviating ADHD, and there is no significant evidence that guanfacine is better than clonidine. (The Hirota *et al.*[31] meta-analysis, though not based on head-to-head comparisons, did not suggest differences in efficacy between the two drugs.)

Clonidine or Guanfacine: Other Considerations

Guanfacine has a somewhat longer half-life (16 hours versus 12 hours), making a once-daily dosage more feasible, although (as discussed below) a twice-daily dosage may be preferable if using either IR form, to reduce peak plasma levels. Guanfacine has a greater risk of interactions with other medications, specifically with drugs that inhibit or induce 3A4 activity. With either drug, blood pressure should be monitored, especially if related symptoms (e.g., dizziness) occur.

In some respects, it would not be difficult to determine whether guanfacine is better than clonidine. A relatively small inexpensive crossover study might clarify the question, but no funding source seems to be motivated to conduct such a study.

Immediate Versus Extended-Release

The differences between IR clonidine and guanfacine and the ER forms require some additional discussion, with digressions. Although the studies that were conducted to obtain FDA approval for ADHD for the two ER medications provide useful information to physicians, and although the drug companies involved clearly hope that FDA approval for these slow-release preparations will foster prescriptions of these medications (rather than the IR generics), it is not hard to argue that the immediate-release generics (which are considerably less expensive) are equally effective and probably do not have significantly increased side effects, if the dosage is modified somewhat.

Pharmacokinetics

FDA-approved labeling[14] focuses on the difference in maximum plasma levels (C_{max}) after a single dose of the ER form versus a single dose of the IR form. For guanfacine, for example, the peak level with the ER form is only about 40 percent of the peak with the IR form. Both types are recommended for once-daily dosage,[14] but if the dose of the IR is divided in half, given as twice-daily dosage, the peak plasma level of the IR (after a single dose) would be reduced by about 50 percent, close to the peak level with the ER.

In addition, the difference in peak plasma level (between IR and ER) is much less at steady state, after multiple doses (steady state occurs after approximately five half-lives). If, at steady state, IR guanfacine is given twice a day (i.e., the dosage interval (12 hours) is about three-quarters of the half-life), the peak plasma level would be more than twice the peak plasma level after a single dose. (These estimates are based largely on information in Dhillon and Gill[45]). In other words, the peak blood level at steady state is about half from the latest dose and half from accumulated guanfacine in the body. The difference in peak plasma level between the IR and ER forms of the medicine would therefore be reduced proportionately, by about half.

Thus, at steady state, a twice-daily dosage of IR guanfacine is likely to result in plasma levels not much different from a once-daily dosage of the ER (perhaps even within the 15% range which would be allowed for a generic). Also relevant, the bioavailability of the ER (the total amount of guanfacine absorbed) is less than that of the IR (only 58% as much, per FDA labeling[14]). Possibly related to this, FDA labeling[14] for immediate-release guanfacine suggests that doses above 3 mg are rarely more helpful (for hypertension), although for the ER (used for ADHD), doses of up to 4 mg are suggested. So 1 to 1.5 mg of IR guanfacine, given twice-daily, could reasonably be expected to be comparable with 3 to 4 mg of the ER form.

In the case of clonidine, both the IR and the ER are recommended for a twice-daily dosage. As with guanfacine, the half-life is about the same for both dosage forms (about 12 hours), but the C_{max} is lower (of course) with the ER (~50% lower, after a single

dose). Again, at steady state, the percentage difference between C_{max} for the IR and the ER would be considerably less than the difference after a single dose. Also similar to guanfacine, the total amount of medication absorbed is greater for the IR form than for the ER form. (The bioavailability of the ER form is about 25% less.) ER clonidine has been used in amounts of only 0.4 mg per day for ADHD; the dosage for the IR form, which was approved for hypertension, was given (FDA labeling[14]) as generally 0.2 to 0.6 mg per day, but it was noted that dosages of up to 2.4 mg per day have been used (for hypertension). Thus (similar to the situation with guanfacine), it seems likely that generic IR clonidine, given up to 0.3 to 0.4 mg per day in two or even three doses, would be comparable with the ER form.

Again, it should be noted that studies of the ER forms for ADHD have been conducted in children and adolescents, whereas studies for hypertension with the IR forms were, of course, conducted in adults. It is reasonable to think that giving adults with ADHD doses comparable to those used in children with ADHD would be well tolerated (perhaps adults could take higher doses, but these have not been studied sufficiently).

IR versus ER: Other Considerations

One advantage of the IR generic forms of these medications is that they are less expensive. As of 2014, the ER forms cost up to 30 times more than the IR forms. Cost may be a reasonable and relevant concern.

There are, of course, physicians who feel more comfortable prescribing forms of drugs that are FDA approved for a particular indication. One might argue that physicians should prescribe based on the knowledge they have of drugs, including pharmacokinetics, and that for drugs with relatively long half-lives, there is little reason to think that the ER forms are clearly preferable.

Efficacy Compared to Stimulants

Although there is a rationale for using clonidine and guanfacine in prisoners and others with ADHD, it has to be acknowledged that these drugs are not as dramatically helpful as are stimulants (the same can be said for atomoxetine). Although studies show statistically significant benefit from $\alpha 2$ agonists, the available papers do not (in my opinion) adequately discuss the marked difference between benefit from stimulants (which can normalize behavior,[46] at least in children), and the much less dramatic benefit from $\alpha 2$ agonists. A 2003 report[47] on the epidemiology of medication use for ADHD reported that 86 percent of children and adolescents received stimulants, whereas only 7 percent received clonidine (guanfacine was used very seldom at that time). The reduced benefit from $\alpha 2$ agonists is probably why these drugs are more often used concomitantly with stimulants (partly to offset stimulant side effects such as insomnia), rather than alone.[37] Despite quite impressive theoretical and laboratory evidence (e.g., Arnsten *et al.*,[43]) suggesting that guanfacine, as an α-2A blocker, should be the optimal drug for ADHD, it seems, clinically, that patients do not respond dramatically to $\alpha 2$ agonists with remission or greatly reduced symptomatology. Rather, it is more accurate to say that $\alpha 2$ agonists are relatively easy medications to use in a prison setting (certainly less problematic than stimulants), that they may reduce typical ADHD symptomatology somewhat, that they may specifically reduce aggressiveness and other symptoms of conduct disorder more than other ADHD treatments, that they may also have some beneficial effect on anxiety (including symptoms of PTSD), and that they may therefore be worth prescribing to prison inmates with ADHD. Many prison inmates desire sedating medications, and since clonidine and guanfacine (perhaps especially clonidine) are somewhat sedating, they may be readily accepted by prison inmates. Of interest, Lichtenstein *et al.*[48] recently reported that taking medication for ADHD (they did not study $\alpha 2$ agonists, only stimulants and atomoxetine) reduces criminal behavior.

Summary

Clonidine and guanfacine have several advantages over other options for treating ADHD in prison inmates. Neither drug is controlled, and both are somewhat sedating. Given their possible (though unproven) anxiolytic effect, they may also help inmates to be calmer; whether this is related to any ADHD effect is unclear. They do not increase liver enzymes as atomoxetine sometimes does, so no routine liver enzyme checks are needed. The dosage of clonidine IR for ADHD is generally up to 0.4 mg per day, in divided doses. The dosage of guanfacine IR would reasonably be up to 3 mg/day. Although clonidine and guanfacine may not have the dramatically bene-

ficial effect that stimulants have for childhood ADHD, they seem a reasonable option in prison because of their significant benefit (with FDA approval) for symptoms of ADHD and their additional possible anxiolytic and sedative effects. They also may help to reduce impulsive aggressiveness, a common problematic symptom of ADHD in prison. Overall, given the FDA-accepted evidence of efficacy, the lack of abuse potential, and the favorable side-effect profile, α agonists may be the treatment of choice for prison inmates with ADHD.

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