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METHADONE DOSING AND CONVERSION: BE CONSERVATIVE

Over three decades of research have established methadone's safety and efficacy. Methadone has several advantages for use in chronic pain of various origins including: excellent oral bioavailability, ability to be delivered down an NG tube, use in patients with a true allergy to morphine and morphine-derivatives, low risk of accumulation in patients with renal impairment, low rates of drug escalation and drug seeking and low cost. Methadone's primary advantage, an inherently long duration of action, is what makes it particularly attractive. Yet, it is this same property that renders methadone's initiation and dosing complicated. While the pharmacokinetic and pharmacodynamic properties of methadone are not completely understood, it is known that methadone redistributes extensively into muscle and fat tissue after administration resulting in drug accumulation with repeat dosing.

Despite its dosing complexity, methadone can be used safely when the following principles are considered. The optimal dosing strategy has not been established. The best approach is to err on the side of being conservative, i.e. start low and go slow! Methadone typically takes 5-7 days to reach steady state drug levels- upward dosage adjustments should occur no more frequently. The optimal method of conversion to methadone from other opioids has also not been established. It is apparent that the sole use of common equianalgesic dose tables may result in overestimation of the initial methadone dose. Methadone's potency increases with increasing dose of the previous opioid and interpatient variability exists. Some recommend initiating methadone using PRN dosing to determine the optimal dose. Others have developed the following algorithm:[1,2]

1. Total the patient's current opioid dose per day and calculate its morphine-equivalent dose using an equianalgesic dose table.[3]
2. If the morphine equivalent dose (MED) is < 200 mg/d: Begin methadone at 2.5-5 mg q8h.
3. If the MED is 200 mg/d-500 mg/d: Begin methadone at ~ 7% the MED divided q8h.
4. If the MED is > 500 mg/d: Begin methadone at ~ 2.3% the MED divided q8h. Add the same 2.3% MED, while simultaneously reducing the dose of the previous opioid by 1/3 every 5-7 days. Conversion should take approximately 15 days.

The initial dose and titration schedule must be individualized to the patient and clinical setting. Patient-clinician communication should be frequent during this initiation phase. It may be prudent to initially limit each prescription quantity to a 1-week supply to ensure communication. If the patient develops intolerable sedation or other adverse effects, instruct the patient to hold or decrease the next dose and adjust the dosing regimen accordingly. Tolerance to sedation will eventually ensue upon cautious dosing. Severe sedation may be indicative of excessive dosing and should prompt immediate medical evaluation.

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Two New Mental Health Drug Options Reviewed

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Aripiprazole (Abilify)

Aripiprazole (Abilify) is the sixth atypical antipsychotic to enter the marketplace joining clozapine, risperidone, olanzapine, quetiapine and ziprasidone. While aripiprazole offers a unique pharmacologic profile, it is unknown if it offers any true clinical advantages.

The true mechanism of action of aripiprazole is unknown. It is proposed that the efficacy is a result of partial agonist activity at dopamine (D_2) and serotonin ($5\text{-}HT_{1A}$) receptors and antagonist activity at serotonin ($5\text{-}HT_{2A}$) receptors. In vitro data have indicated D_2-agonist activity of aripiprazole at presynaptic autoreceptors, with antagonist activity at postsynaptic D_2 receptors.[1,2,3] These dual effects are unlike those of both conventional and all other atypical antipsychotic drugs.

The activity of aripiprazole is due primarily to the parent drug, however some activity is attributed to its major metabolite dehydro-aripiprazole. Aripiprazole has a long 75-hour half-life (the half-life of dehydro-aripiprazole is 94 hours). Elimination of aripiprazole is primarily hepatic involving the cytochrome P450 2D6 and 3A4 isoenzymes. The half-life of aripiprazole doubles for poor 2D6 metabolizers. No dosage adjustments are needed in the elderly, or those patients with hepatic or renal impairment. Aripiprazole can be taken with or without food. Its bioavailability is 87%. [4]

Because aripiprazole is a substrate for both the 2D6 and 3A4 isosenzymes, the following recommendations have been made for the following significant drug interactions:

- CYP3A4 Inducers (e.g. carbamazepine)—double aripiprazole dose
- CYP3A4 Inhibitors (e.g. ketoconazole)—decrease aripiprazole by half.
- CYP2D6 Inhibitors (e.g.quinidine, paroxetine, fluoxetine)—decrease aripiprazole by half.

The long-term efficacy of aripiprazole in the treatment of schizophrenia has not been well established. There are four short-term (4-6 week) clinical studies available for review (see table 1). Each placebo-controlled trial evaluated the efficacy of aripiprazole in acutely relapsed schizophrenic inpatients. One study failed to demonstrate efficacy superior to placebo. Three studies included an active control (haloperidol or risperidone), however, it is important to realize that these studies were not designed to compare aripiprazole with the active comparators, only to placebo.

Table 1. Short-term aripiprazole clinical trials

Study Description	Pop	Daily Dose	Clinical outcome	Comments
R, DB, PC aripiprazole & haloperidol vs. placebo[5] 4 weeks	N=414 Acutely relapsed inpatients	15, 30mg (H=10mg/d)	Superior to placebo for PANSS, PANSS (+) and CGI	Only the 15mg strength was superior to placebo for the PANSS (-).
R, DB, PC aripiprazole & risperidone vs. placebo[6] 4 weeks	N=404 Acutely relapsed inpatients	20, 30mg (R=6mg/d)	Superior to placebo for PANSS, PANSS (+), PANSS (-), and CGI	Did not actively compare aripiprazole to risperidone.
R, DB, PC aripiprazole vs. placebo[7] 6 weeks	N=420 Acutely relapsed inpatients	10, 15, 20mg	Superior to placebo for PANSS, PANSS (+) and PANSS (-)	Higher doses offered no advantage over 10mg daily dose.
R, DB, PC aripiprazole & haloperidol vs. placebo[7] 4 weeks	N=103 Acutely relapsed inpatients	5-30mg range (H=5-20mg/d)	Placebo superior to aripiprazole on BPRS. Aripiprazole superior to placebo for CGI only.	Demonstrated lack of superiority over placebo.

DB=double-blind, PC=placebo-controlled, H=haloperidol, R=risperdone, CGI = Clinical Global Impression Scale, BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale

Common side effects (incidence ≥10%) reported during clinical trials included: headache, nausea, vomiting, constipation, anxiety, insomnia, lightheadedness, somnolence, and akathisia. Aripiprazole has minimal effects on weight and cardiac conduction.

Conclusions

Aripiprazole is an atypical antipsychotic with a unique pharmacologic profile. Its place in therapy has not been fully elucidated, however it may be useful in patients who experience a lack of efficacy, weight gain, or cardiac conduction abnormalites with other agents in this class. The cost of aripiprazole (~$260/month), in addition to its increased incidence of anxiety and akathisia will prevent the use of this drug in some patients.

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Atomoxetine (Straterra)

Atomoxetine (Straterra) is the newest medication approved for the treatment of attention-deficit hyperactivity disorder (ADHD). Although atomoxetine was only recently approved by the Food and Drug Administration (November 26, 2002), research for this product has spanned two decades, two trade names and two indications. First labeled tomoxetine, the drug was evaluated for antidepressant properties. At well-tolerated doses, this selective norepinephrine uptake inhibitor failed to demonstrate efficacy as an antidepressant.

Stimulant medications (including methylphenidate preparations and dextroamphetamine preparations) are considered first-line agents for the treatment of children (greater than six years of age) with ADHD. Atomoxetine is the first medication approved for the treatment of ADHD that is not a stimulant. Though its true mechanism of action is unknown, it is thought to be related to the selective inhibition of the presynaptic norepinephrine transporter.

Elimination of atomoxetine is primarily hepatic involving the cytochrome P450 2D6 isoenzyme (drug interactions may be seen with 2D6 inhibitors). Its 4 to 5.2 hour half-life is extended to 21.6 hours in poor 2D6 metabolizers. The drug can be taken with or without food. The pharmacokinetics of atomoxetine are similar between children, adolescents and adults. The drug has not been evaluated in the geriatric population or in children less than 6 years of age.

Atomoxetine is dosed according to weight. Dosage adjustment is recommended in patients with moderate or severe hepatic insufficiency. Normal dosing can be used in patients with end stage renal disease or lesser degrees of renal insufficiency.

Atomoxetine's clinical efficacy has been proven in several randomized placebo-controlled trials of children (greater than 6 years of age), adolescents, and adults. Several important clinical considerations supported by the outcomes of these trials include:

- The optimal dose for children and adolescents appears to be 1.2mg/kg/day.
- Available studies are unable to prove efficacy of once daily dosing.
- Atomoxetine's antidepressant efficacy is not superior to placebo.
- Significant increases in heart rate and decreases in body weight have been observed and appear to be dose-related.
- Common adverse effects in adult patients include: dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, dizziness, erectile dysfunction and sweating.

Atomoxetine appears to have a significant and dose-related effect on growth. In clinical trials, atomoxetine-treated patients lost an average of 0.4 kg in weight and gained 0.9 cm in height while placebo-treated patients gained an average 1.5 kg and 1.1 cm.[3] The manufacturer recommends monitoring growth during treatment. The FDA has asked Eli Lilly for additional information regarding this adverse effect.

Atomoxetine has not been studied in children less than six years of age. Long-term efficacy has not been established for the treatment of children (beyond 9-weeks) and adults (beyond 10-weeks). In addition, there are no randomized double-blind controlled trials evaluating the efficacy of atomoxetine compared to stimulant medications (one open-label trial is available for review).[5]

Conclusions

Atomoxetine is the first non-controlled substance approved for the treatment of ADHD. One advantage of using a non-controlled substance is the need for only one prescription per year. Efficacy compared to first-line stimulant medications, however, has not been proven in blinded head-to-head randomized controlled clinical trials. In addition, atomoxetine should be considered second-line based on its cost (~$90/month), the need for BID dosing, and the potential adverse effect on growth.

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Table 2. Atomoxetine Clinical Trials

Description	Duration	Population (n)	Daily Dose	Clinical Outcome
DB, PC, dose-response study[1]	8 weeks	N=297 aged 8 to 18	0.5, 1.2, 1.8 mg/kg/day divided early AM and late afternoon/early evening	Primary outcome measure= ADHDRS 2 higher doses improved ADHD sx > placebo. 1.8mg/kg/day dose provided no additional benefit over 1.2 mg/kg/day dose.
R, DB, PC, acute treatment study[2]	6 weeks	N=171 aged 6 to 16	Titrated on a weight-adjusted basis according to clinical response to a max of 1.5 mg/kg/day administered as a single AM dose. Mean final dose was 1.3mg/kg/day	Statistically significant improvement over placebo as measured by the ADHDRS scale. Treatment effect size = 0.71
Acute, R, DB, PC study[6]	9 weeks	N=147 aged 7 to 13	Titrated based on weight and response to a max dose of 2.0mg/kg/day. Mean final dose was 1.6mg/kg/day.	Statistically significant improvement over placebo as measured by the ADHDRS scale.
Acute, R, DB, PC study[6]	9 weeks	N=144 aged 7 to 13	Titrated based on weight and response to a max dose of 2.0mg/kg/day divided in early morning and late afternoon doses. Mean final dose was 1.6mg/kg/day	Statistically significant improvement over placebo as measured by the ADHDRS scale.
Acute, R, DB, PC study[4]	10-week	N=280 aged 18 and older	60-120mg/day. Mean final dose 95mg/day.	Statistically significant improvement over placebo as measured by CAARS
Acute, R, DB, PC study[4]	10-week	N=256 aged 18 and older	60-120mg/day. Mean final dose 95mg/day.	Statistically significant improvement over placebo as measured by CAARS

R=randomized; DB=double-blind; PC=placebo-controlled, ADHDRS = ADHD Rating Scale-IV-Parent Version, CAARS=Conners Adult ADHD Rating Scale Screening Version

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