Automatic therapeutic substitution in a psychiatric hospital
Amy M. VandenBerg, PharmD, BCPP

1Department of Pharmacy Services, Medical University of South Carolina, Charleston, SC

ABSTRACT
Automatic therapeutic substitution protocols have become common practice in health care systems in the last ten to fifteen years. These protocols can help formulary management, simplify pharmacy inventory, and reduce costs. To date, psychotropics continue to be absent from the most common automatic substitution policies. This article will describe the rationale for select psychotropic substitutions.

KEYWORDS
automatic therapeutic substitution, psychotropic, formulary

INTRODUCTION
The concept of automatic therapeutic substitution (ATS) is not new to health care systems. For over a decade, it has been commonplace for hospitals to have a limited formulary with regard to ACE inhibitors, proton pump inhibitors and H2 antagonists. Rather than stock up to twelve agents in a class of medications, institutions may opt to automatically substitute one product for all. The benefits to such a system include decreasing costs through decreased total inventory and decreased acquisition costs (either by choosing the least expensive alternative or contract pricing for using only one product).

One group of medications that has often been left out of ATS protocols is psychotropics. With the exception of benzodiazepines, surveys support a reluctance to substitute psychotropics. Ten years ago, this hesitancy made sense. While there were multiple agents within a class (e.g., serotonin reuptake inhibitors and second generation antipsychotics), each was different in structure, binding affinity, metabolism and side effects, while similar in cost. However, in recent years, many new psychotropics have been 'cousins' of previously released medications, generally released at the end of the patent life of the predecessor medication. These include single isomers, extended-release formulations, prodrugs and active metabolites. These 'new' agents are often similar to their predecessors with regard to mechanism of action, binding affinity, and adverse effects. Comparative efficacy studies are often not available; however, cost differences can be significant with loss of patent exclusivity. If the concept of ATS is based on similarities in mechanism, efficacy, side effects and therapeutic uses, then it would make sense to consider these 'new' psychotropics for ATS.

The Medical University of South Carolina-Medical Center (MUSC-MC) has over twenty inpatient ATS protocols spanning medication classes from ACE inhibitors to H2-antagonists to antimicrobials and, starting in 2006, psychotropics. Nearly one third of the ATS protocols at MUSC-MC are for psychotropic agents. All of the ATS protocols are developed in collaboration with clinical pharmacy specialists and physicians practicing in the therapeutic area. They are then approved by various committees including Pharmacy and Therapeutics and Medical Executive Committees. In keeping with American College of Clinical Pharmacy guidelines, prescribers are notified about the interchanges and exceptions are permitted at the request of the prescriber.

An internal survey of MUSC-MC psychiatry prescribers was conducted in 2008 to gauge the level of acceptance of various substitutions. The products included in the survey were citalopram/escitalopram, bupropion (various formulation substitutions), venlafaxine/desvenlafaxine, paliperidone/risperidone, quetiapine immediate/extended release, as well as traditional ATS agents (H2 antagonists, proton pump inhibitors, ACE inhibitors and non-sedating antihistamines). Each interchange had one or more specific dose conversions listed for survey respondents to indicate whether they would approve of that specific interchange (yes or no). The prescribers had similar acceptance ratings for psychotropic interchanges as for the non-psychotropic interchanges (55%-75% for specific doses). The lowest rating was for desvenlafaxine/venlafaxine, which was a relatively new product at that time, with 31% of prescribers responding that none of the interchanges listed were appropriate. However, free text comments in the survey indicated a desire for more education regarding a potential venlafaxine/desvenlafaxine interchange. For the other psychotropic classes, 13% or fewer prescribers indicated...
that none of the interchanges were appropriate, indicating greater than 85% acceptance of psychotropic ATS in concept.

To date, no significant adverse event or adverse clinical outcome associated with any of these ATS protocols has come to light. The MUSC-MC P&T newsletter provides education when new ATS protocols are approved. On an annual basis, the clinical pharmacy specialists in psychiatry educate prescribers, nurses and pharmacy staff regarding the active psychotropic ATS protocols. All ATS interchanges provide 'pop-up' notifications in the computerized prescriber order entry system and show up as administration instructions for nurses on the electronic medication administration record. Protocols are evaluated for internal quality assurance and updated based on current evidence as needed.

This article will discuss potential ATS protocols for psychotropics and provide additional background and rationale for select protocols. It is beyond the scope of this article to provide the complete evidence for each proposed ATS. Additionally, specific dose interchanges will not always be delineated. This article should serve as a guide for agents that may be further evaluated for ATS at your institution.

**SIMILAR PRODUCTS WHICH ARE NOT AB RATED**

When comparing similar agents that are not AB rated due to differences in dosage form (e.g., tablet vs capsule) or concentration (e.g., 5 mg/mL vs 2 mg/mL) the key is to look at the differences and similarities that do exist. Pharmacokinetic parameters can easily be gleaned from the package insert for products to compare half-life, area under the curve, C_max and t_max. If pharmacokinetic parameters are similar, use clinical judgment to decide whether differences in formulation are likely to have clinical or logistical significance.

**Hydroxyzine**

Hydroxyzine is available in two different salt formulations for oral use, pamoate (Vistaril®) and hydrochloride (Atarax®). Each oral formulation has similar FDA approved indications and is available as 25 mg and 50 mg capsules or tablets. Published literature on hydroxyzine for treatment of anxiety does not specify salt form. Additionally, injectable hydroxyzine is only available as the hydrochloride salt form. The primary difference between the two products that does not allow for AB rating is that the hydrochloride is available as a tablet or 10 mg/5 mL syrup while the pamoate salt is available as a capsule or 25 mg/5 mL suspension. Tertiary references do not differentiate products when listing pharmacokinetic parameters. To accommodate lower doses in the pediatric population, reduce the risk of an inadvertent overdose with the suspension product, and to keep the injectable product consistent with the oral product our institution opted to stock only the hydrochloride formulations of hydroxyzine. Since the acquisition cost is similar, this ATS does not significantly reduce cost, however inventory space may be reduced.

**Venlafaxine**

Venlafaxine is available as immediate-release tablets, extended-release tablets (VERT), and extended-release capsules (VXRC). VERT was FDA approved in 2008 after the immediate-release tablets were generically available, but prior to the release of generic VXRC. VERT was a unique product that had the same active ingredient as VXRC and nearly identical pharmacokinetics compared to VXRC. However, because the dosage form was a tablet rather than a capsule, the two were not considered AB rated equivalents.

Both before and after generic immediate-release venlafaxine was available, the preferred agent for our prescribers was VXRC due to once daily dosing. At the time VERT was released, VXRC still had patent exclusivity and was significantly more expensive. Based on the similarities in pharmacokinetic parameters, we instituted an ATS converting all orders for venlafaxine to VERT. At the time, we still had paper orders and the ATS also helped decrease calls to clarify orders for once daily venlafaxine or "Effexor" that did not specify extended release on the order. All products are now available generically, and the current AWP price for generic VXRC is less than VERT so our institution is updating this ATS to convert all orders to VXRC.

**ACTIVE METABOLITES, SINGLE ISOMERS AND PRODRUGS**

The last decade has seen a significant increase in active metabolites (desvenlafaxine, paliperidone), single isomers (escitalopram, armodafanil, levomilnacipran) and prodrugs (lisdexamfetamine). These products are generally released towards the end of patent life of the 'predecessor' (parent drug, racemic mixture or active metabolite, respectively). As such, they are generally much more expensive compared to the predecessor.

When considering these types of similar products for ATS, it is important to evaluate first and foremost whether there are clinically significant differences in pharmacokinetics or pharmacodynamics. With select older psychotropic medications, it is clear that active metabolites may have clinically significant differences.
For example, the receptor binding profile of amitriptyline significantly changes when it is metabolized to nortriptyline. Imipramine binding, similarly, changes when it is metabolized to desipramine. Diazepam is significantly different than the active metabolite oxazepam with regard to metabolism, t\text{max} and t\text{1/2}. Differences in pharmacokinetics or receptor binding do not necessarily rule out an ATS protocol, but variances must be carefully evaluated for clinical significance.

Next, consider any and all evidence for differences in efficacy between products. Head to head trials are often not available to directly compare the new agent to the predecessor. Comparing the two agents may require reviewing separate trials of the two agents with regard to efficacy outcomes, dosing and adverse events, then using clinical judgment to determine if there are theoretical or actual benefits with one product over another.

**Venlafaxine/Desvenlafaxine**

Desvenlafaxine, the active metabolite of venlafaxine, was released in 2008 as extended release tablets (DERT). The two products (DERT and VXRC) have very similar pharmacokinetics and nearly identical pharmacodynamics. Per the package insert for Effexor XR®, venlafaxine and desvenlafaxine are "pharmacologically approximately equiactive and equipotent." One could argue that it would be clinically appropriate to develop an automatic therapeutic substitution for DERT to VERT or now generically available VXRC. The available dosage strengths are somewhat limiting, however. Desvenlafaxine extended release tablets are available in 50 mg increments while venlafaxine extended release products are available in 37.5 mg increments. Based on AWP pricing, treating 100 patient days on desvenlafaxine 150 mg vs. venlafaxine 150 mg would be over $1700 difference in cost. While pharmacokinetic and pharmacodynamic comparison suggests the products would be dose equivalent, the approved dose range of 50-100 mg for DERT is significantly different than VXRC 37.5-225 mg. The cost difference makes this ATS worthy of further evaluation.

**Risperidone/Paliperidone**

Risperidone has been on the market since 1993, and became generically available in 2008. The active metabolite of risperidone, 9-OH-risperidone, was released as paliperidone in 2006. Paliperidone is an extended-release formulation which utilizes osmotic pump technology for continuous release, which minimizes C\text{max}. There are no published head-to-head trials of the two products. The primary differences in pharmacokinetics have to do with bioavailability, C\text{max} and half-life. Additionally, there are differences in metabolism between the two agents, with risperidone more dependent on CYP 2D6 for metabolism. The receptor binding profile of the two products are very similar. At current AWP, the cost savings from an ATS would range from $2162 to $3618 for 100 patient days of risperidone converted from paliperidone depending on dose.

**Single Isomers**

Single isomer products generally tout one of two ‘benefits’ over racemic mixtures. First, that the inactive isomer has been removed therefore the single isomer is more potent. While true, this may also just mean that the dose is lower because 50% of the drug was isolated. Inactive isomers may also be implicated in side effects, impeding the action of the active isomer, and differential pharmacokinetics. When comparing racemic products to single isomers, it is essential to determine if there is evidence to support a clinical consequence of any differences. For example if a racemic mixture has 70% protein binding and the single isomer has 60% protein binding, there is variability. However, the difference is unlikely to be clinically significant.

**Citalopram/escitalopram**

Citalopram has been on the market since 1998. The s-isomer of citalopram, escitalopram was released in 2002. At the time of release there were no head to head trials, although there were studies that used citalopram as an active comparator. Citalopram became generically available in 2004. While there was some debate regarding the comparative doses, at the most basic level, removing 50% of the drug by isolating one isomer, would result in a 2:1 dose ratio. With the FDA warning of 2011, the interchange between these two agents is up for discussion again. Although it is beyond the scope of this article to discuss the clinical importance of any QTc prolongation that may occur with citalopram, it may be prudent in light of the warning to implement a reverse ATS with escitalopram as the preferred option. To date, there are still no compelling head to head trials comparing the two agents, and conventional wisdom tells us their efficacy is similar. Since escitalopram is now generically available, the cost savings associated with citalopram is minimized, especially if practitioners increase monitoring of electrolytes and electrocardiograms with citalopram.

**Milnacipran/levomilnacipran**

Milnacipran has been marketed outside the United States for major depressive disorder since 1996. It was approved...
in 2009 in the US only for the treatment of fibromyalgia. In 2013, levomilnacipran was approved by the FDA for the treatment of MDD. It is the single, 1S, 2R- isomer of milnacipran. At this time, there are no head to head trials between the two products. Milnacipran is available as 12.5 mg, 25 mg, 50 mg, and 100 mg tablets. \[17\] Levomilnacipran is available as 20 mg, 40 mg, 80 mg and 120 mg extended release capsules. \[18\] The \(t_{\text{max}}\) and half-life are longer for levomilnacipran (6-8 hours and 12 hours) compared to milnacipran (2-4 hours and 6-8 hours), as expected with the extended-release formulation. However, bioavailability for both agents is close to 90%, and both are predominantly eliminated unchanged in the urine. \[17,18\] As with desvenlafaxine, interchange may be difficult due to the differences in available dosage strengths.

**EXTENDED-RELEASE PRODUCTS**

Extended release products are the most common form of re-release or re-branding of psychotropic agents. From antidepressants (paroxetine, fluvoxamine) to antipsychotics (quetiapine) to benzodiazepines (alprazolam) to mood stabilizers (carbamazepine, lithium, valproate) to stimulants (amphetamines and methylphenidate), all classes of psychotropics have had numerous formulations (immediate-release VPA, extended-release VPA capsules, extended-release VPA capsules, VPA syrup, delayed-release divalproex tablets, divalproex capsules, and extended-release divalproex tablets). At one time "Depakote" was synonymous with the delayed-release tablets, however the extended-release tablets, released in 2000, introduce a potential for confusion between products. These products have differences in pharmacokinetics including bioavailability, \(C_{\text{max}}\), \(t_{\text{max}}\) as well as \(t_{\text{min}}\). \[19,20\] There is literature to help guide conversion between the divalproex tablet products. \[21\] As all of these products are currently available as generic agents (except Stavzor), the primary rationale for an ATS protocol would be tolerability, consistency of treatment, and patient safety.

Pharmacokinetic differences between immediate- and extended-release products are key when developing ATS protocols. Differences in absorption or bioavailability (e.g., delayed-release vs extended-release divalproex, paroxetine immediate vs controlled-release) may require a dose adjustment between products. Rate of absorption may impact dosing schemes if side effects are peak related and there are significant differences in \(C_{\text{max}}\) or \(t_{\text{max}}\). Since the active component is the same, generally differences in metabolism, elimination or drug interactions are not an issue.

**Bupropion**

Bupropion is now available in five different formulations (immediate-release tablets, sustained-release tablets [Zyban and Wellbutrin], extended-release tablets, 450 mg extended-release tablets and extended-release tablets of the hydrobromide salt form). Additionally, bupropion has the branded-generic product Budeprion, which is available as sustained- and extended-release tablets. The different formulations can lead to confusion in ordering on the part of the prescriber. While computerized order entry systems can help with prompts, these systems are not fail-safe. Confusion regarding product selection and appropriate ordering became a patient safety concern. Our institution opted to carry the SR formulation and convert all orders to the appropriate dosing. Therefore, "Wellbutrin 300 mg daily" would be changed to SR 150 mg BID. This minimizes the risk of a patient receiving immediate-release bupropion 300 mg as a single dose. (Single doses of immediate release bupropion are not recommended to exceed 100 mg due to seizure risk). It also minimizes the need for calls to the prescriber to clarify the intended product.

**Valproic Acid/Divalproex**

Similar to bupropion, valproic acid (VPA) is available in numerous formulations (immediate-release VPA capsules, extended-release VPA capsules, VPA syrup, delayed-release divalproex tablets, divalproex capsules, and extended-release divalproex tablets). Among the tools that have become more popular in the past two decades is the process of automatic therapeutic substitution. Estimates from the early 1980s indicated that fewer than 50% of hospitals stocked single products in class and only 31% allowed therapeutic substitution. \[3\] By 1998, 84% of hospitals surveyed employed some form of therapeutic interchange. \[3\] While more recent surveys are not available in the literature, ATS appears to remain a common practice across the country. There still is a paucity of literature regarding ATS for psychotropic medications. However, we have found that these protocols can be well received when developed and implemented appropriately. Increased focus on cost containment and cost savings in healthcare may make these protocols more important to consider in future practice.

**CONCLUSION**

There are a number of strategies for formulary management outside of having a closed formulary. Among the tools that have become more popular in the past two decades is the process of automatic therapeutic substitution. Estimates from the early 1980s indicated that fewer than 50% of hospitals stocked single products in class and only 31% allowed therapeutic substitution. \[3\] By 1998, 84% of hospitals surveyed employed some form of therapeutic interchange. \[3\] While more recent surveys are not available in the literature, ATS appears to remain a common practice across the country. There still is a paucity of literature regarding ATS for psychotropic medications. However, we have found that these protocols can be well received when developed and implemented appropriately. Increased focus on cost containment and cost savings in healthcare may make these protocols more important to consider in future practice.
REFERENCES


16. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. [3-12-2012]


How to cite this editor-reviewed article