

**Practical Guidelines for the Use of Medications with
Anticholinergic Activity and Benztropine
in Adult Individuals with Intellectual Disabilities**

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Abstract

The development of these guidelines on the use of medications with anticholinergic activity in adult individuals with intellectual disabilities (IDs) was approached pragmatically. The guidelines have been developed using the prescribing information and reviewing the available literature on relevant neuropsychiatric disorders in populations without ID. Given the dearth of available literature on the ID populations, one must extrapolate from available studies. Our knowledge of the pharmacokinetic and pharmacodynamic mechanisms of these drugs has been obtained from studies of other neuropsychiatric disorders. This limited knowledge was used for developing a personalized medicine approach in individuals with IDs, and providing recommendations on the use of these drugs.

The first guideline focuses on the pharmacology of all medications with anticholinergic drugs and their risk for cognitive deficits and other adverse drug reactions (ADRs). It provides lists of drugs with definitive or possible antimuscarinic activity. Practical sections focus on the definition and documentation requirements for “polypharmacy of drugs with anticholinergic activity” (≥ 2 drugs with definitive anticholinergic activity) and “other situations with potential risk of polypharmacy with drugs with anticholinergic activity”. The second guideline focuses on benztropine with its indications, contraindications, personalized dosing and ADRs. Drug utilization reviews (DURs) have been used to improve the quality of drug therapy. A DUR was developed, which includes the crucial practical aspects of the first guideline with a section on polypharmacy of drugs with anticholinergic activity and a section on other situations with potential risk of polypharmacy with drugs with anticholinergic activity. DURs for oral and parenteral benztropine are also provided.

The procedures contained in these guidelines may not fully account for all of the possible risks of treatment in this population because of the limited studies available; thus, there will be a need to periodically update this guide as new knowledge becomes available. Nevertheless, we believe that these guidelines will provide a useful resource for clinicians who treat adult individuals with IDs.

Keywords: anticholinergic; antipsychotic agents; benztropine; cholinergic antagonists; intellectual disabilities; muscarinic antagonists.

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1. Introduction

The development of these guidelines on anticonvulsants and mood stabilizers for individuals with intellectual disabilities (IDs) was approached pragmatically, as were prior guidelines on clozapine (Sabaawi et al., 2006), and other second-generation antipsychotics (de Leon et al., 2009). Thus, the reader needs to be aware that these guidelines have been developed using the prescribing information and reviewing the available literature on relevant neuropsychiatric disorders in populations without ID. Given the dearth of available literature on the ID populations (see sections 1.1.1. and 1.1.2.), one must extrapolate from available studies. The limitations of such an approach and the cautious skepticism one must maintain when leaving the terra firma of evidence-based medicine are not lost on the authors and are encouraged in the reader.

From a strict pharmacological point of view, all of these drugs with anticholinergic activity are more properly described as “drugs with antimuscarinic activity” or “antimuscarinic drugs” since they are muscarinic antagonists (de Leon, 2011). These drugs block muscarinic receptors, one of the two main types of cholinergic receptors. The first guideline (Section 2) focuses on all medications with anticholinergic activity and their risk for causing cognitive deficits. The second guideline (Section 3) focuses on benztropine, one of the anticholinergic drugs used as an antiparkinsonian. The structure of this guideline for an individual drug follows a pattern similar to that of the guidelines of individual drugs previously published (de Leon et al., 2009; Sabaawi et al., 2006).

In this introduction, three concepts, evidence-based medicine, personalized medicine and drug utilization reviews (DURs), are briefly reviewed in reference to how they have been utilized in these guidelines. In the evidence-based medicine section the computer searches used in developing these guidelines are described. The personalized medicine section focuses on how the knowledge of pharmacokinetic and pharmacodynamic mechanisms can be used to personalize prescription and how this was used to develop these guidelines. The DURs contain the most important and clinically relevant elements described in the guidelines.

1.1. Evidence-based medicine

Prior guidelines (de Leon et al., 2009) explain in detail that we live in the era of evidence-based medicine. However, treatment information provided by evidence-based medicine is

systematically biased by pharmaceutical company bias and by lack of evidence as it relates to chronic conditions (Hope, 1995; Lowey, 2007). These limitations are particularly relevant for the treatment of individuals with ID. Pharmaceutical companies rarely conduct clinical trials in individuals with IDs, and adults with IDs are excluded from psychiatric clinical trials.

In a practical guideline which attempts to summarize information from complex literature for clinicians, one undeniably runs the risk of making arbitrary statements. If the reader feels that some of the statements are arbitrary, he/she needs to understand that these statements were intended to establish a framework for clinicians. This framework is not intended to replace but to augment individual judgment and clinical expertise. Moreover, the field continues to evolve and emerging literature may become available following the authors' final review of the most recent articles available in the fall of 2010.

1.1.1. Evidence-based medicine for medications with anticholinergic activity

The antimuscarinic potency of many drugs has not been systematically studied; there is no easy way to compare their antimuscarinic potency. The literature provides nine types of articles/studies (de Leon, 2011): 1) *in vitro* muscarinic receptor binding studies; 2) *in vivo* brain imaging studies; 3) animal models; 4) *in vivo* studies of serum anticholinergic activity (SAA) measured by radioreceptor assay (RRA) in patients; 5) *in vitro* studies after adding a drug to serum and measuring anticholinergic activity by RRA; 6) patient studies of antimuscarinic adverse drug reactions (ADRs), focused on one drug; 7) volunteer studies of antimuscarinic ADRs, focused on one drug; 8) article reviews with lists of antimuscarinic drugs; and 9) scales that quantify antimuscarinic activity. Due to varying methods and differing validity/reliability of the results, it is not possible to establish an evidence-based approach to review these studies (de Leon, 2011) but this guideline tries to combine them in a comprehensive approach that reflects the complexity of the data. *In vitro* affinity studies are a good starting point since there is no clear information that a drug can bind to muscarinic receptors in concentrations used in clinical practice and has a antagonist profile; it is hard to be sure that the drug is a muscarinic antagonist. The SAA study by RRA is probably one of the most sophisticated methods used to determine which drugs may have peripheral ADRs. However, even these studies have limited agreement concerning drugs that may have low or questionable

antimuscarinic activity; low levels of SAA in patients analyzed using RRA may reflect nonspecific binding rather than antimuscarinic activity (de Leon et al., 2003). An influential article (Tune et al., 1992) using RRA provided a long list of drugs with low activity which are not traditionally considered antimuscarinic. However, for many of these drugs not traditionally considered antimuscarinic, there are no *in vitro* studies indicating binding to these receptors. In a more recent and sophisticated study adding drugs in different concentrations to serum, Chew et al. (2008) found that some of these drugs may have no relevant antimuscarinic activity.

One main reason for developing a guideline for the use of drugs with anticholinergic activity in individuals with ID is their association with cognitive deficits. Antimuscarinic drugs are some of the most frequent causes of delirium in the elderly (Mintzer & Burns, 2000; Penttilä et al., 2005; Peters, 1989). There are no studies in the literature of the cognitive deficits presumably associated with the use of antimuscarinic drugs in patients with IDs. A PubMed computer search on 9/2/10 using "anticholinergic drug" AND ("mental retardation"[Mesh] OR "autistic disorder"[Mesh] OR "developmental disabilities") produced two articles that did not provide relevant information on cognitive deficits in this population. Twenty-one articles were found when the search used "anticholinergic" AND ("mental retardation"[Mesh] OR "autistic disorder"[Mesh] OR "developmental disabilities"), but none provided relevant information on cognitive deficits. The geriatric literature provides many studies indicating the use of anticholinergic medications; particularly, polypharmacy with drugs with antimuscarinic activity is associated with cognitive deficits and even with episodes of delirium or confusion. Some of these geriatric studies are supported by serum anticholinergic activity measures using radioreceptor assay (Campbell et al., 2009; Mulsant et al., 2004; Tune & Egeli, 1999; Tune et al., 1992). Some schizophrenia studies also support drug anticholinergic activity as a partial explanation of some of the cognitive deficits in schizophrenia (Minzenberg et al., 2004; Vinogradov et al., 2009). In summary, although no studies in individuals with IDs have been conducted to demonstrate the association between polypharmacy of antimuscarinic drugs and impaired cognition, studies in other patients with impaired cognition, such as the elderly and schizophrenia patients, suggest that impaired cognition may be possible and it is better to be cautious with polypharmacy of antimuscarinic drugs in individuals with IDs.

1.1.2. Evidence-based medicine for benztropine

In these guidelines (Section 3), benztropine was selected as an example of an anticholinergic with antiparkinsonian properties. Benztropine is probably the anticholinergic with antiparkinsonian properties most frequently used by US psychiatrists. It has the advantage of having both oral (Par Pharmaceuticals, Inc., 2005; Upsher-Smith Laboratories, Inc., 2002) and parenteral formulations (Nexus Pharmaceuticals, Inc., 2009). Biperiden and trihexyphenidyl are only available in oral form in the US. Other alternatives for treating antipsychotic-induced extrapyramidal symptoms (EPS) are the dopamine-releasing agent, amantadine, and the antihistamines with high antimuscarinic activity, diphenhydramine or promethazine. In the US the parenteral formulations of these two antihistamines are much cheaper than the parenteral formulation of benztropine (Satterthwaite et al., 2008). Ideally, a benztropine guideline for using this compound on individuals with IDs should use an evidence-based approach; unfortunately the literature is very limited. A PubMed computer search on 10/2/10 using "benztropine"[Mesh] AND ("mental retardation"[Mesh] OR "autistic disorder"[Mesh] OR "developmental disabilities") produced 9 articles. When it was limited to "All Adults (19+ years)" 7 articles were provided, including a double-blind placebo-controlled study for drooling (Camp-Bruno et al., 1989); the rest were mainly case reports about the use of benztropine in individuals with ID. In summary, no studies have been conducted in individuals with IDs to study benztropine use in Parkinson's disease or antipsychotic-induced EPS. A pragmatic approach suggests that limited scientific information coming from other relevant neuropsychiatric disorders in other populations is better than no information. As most of the information is extrapolated from other neuropsychiatric disorders, it makes no sense to grade the level of evidence according to evidence-based criteria.

Using another antiparkinsonian instead of benztropine as first choice for treating individuals with ID would require developing a new guideline by using this benztropine guideline as a template and modifying the dosing and drug-drug interaction (DDI) sections.

1.2. Personalized prescription using pharmacological mechanisms

Evidence-based approaches may never work particularly well in IDs. Personalizing the treatment in these individuals is even more crucial than in other areas of medicine. Devinsky (2002) emphasized very well how the heterogeneity of patients with ID makes generalization difficult.

Although personalized prescription is usually considered equivalent to using genetics to personalize drug prescription, the first author prefers the concept of personalized prescription and uses it with implications beyond pharmacogenetics, including all scientific information valid for prescribing medication (de Leon, 2008; 2009). Genetics may not be crucial for all drugs; therefore, in this comprehensive view clinicians must consider genetic, environmental and personal variables when prescribing medication and incorporate some basic pharmacological principles (de Leon, 2008; 2009).

De Leon (2009) proposes that personalized prescription in the clinical environment can be expressed in two main ways: as personalized drug selection and as personalized dosing, both of which are conceptually embedded into these guidelines. Taking into account relative contraindications and ADRs described in the guidelines, clinicians can begin personalizing drug selection. Moreover, these guidelines pay particular attention to personalized dosing by focusing on how environmental variables such as DDI or personal variables such as aging or renal impairment may impact dosing.

To understand personalized prescription drug actions need to be separated in drug efficacy and drug safety. Drug efficacy refers to the desired effect while drug safety refers to ADRs. A drug's pharmacokinetic and pharmacodynamic mechanisms are behind its efficacy and safety. Moreover, genetic, environmental and personal variables influence drug pharmacokinetic and pharmacodynamic mechanisms and through them its efficacy and safety (de Leon, 2010; 2011). Section 2.5 explains how pharmacological knowledge can be used to make predictions about how pharmacokinetic DDI may potentiate antimuscarinic effects. Although there are no systematic studies on the effect of pharmacokinetic DDI on ADRs of antimuscarinic drugs, a few case reports and, more importantly, the pharmacological mechanisms indicate that this may be an area of concern of which clinicians need to be aware and which requires further investigation.

1.3. Drug utilization reviews

It may be difficult to conceptualize how these pharmacological guidelines can be implemented in the real world. Thus, we have developed three DURs (Appendices 1-3). Each DUR contains the most important and clinically relevant elements described in the corresponding guideline. Our experience with prior guidelines is that DURs help clinicians by providing a simple, quick, and graphic method when considering the crucial issues related to each guideline.

DURs were developed in the 1980s and implemented in the 1990s to improve the quality of drug therapy for ambulatory Medicaid patients in the US. More recent literature suggests that traditional retrospective DURs are not effective in preventing DDIs (Peng et al., 2003); they can only document them after the fact. Prospective DURs involve reviewing each prescription for an individual patient before it is dispensed to identify DDIs, contraindications, therapeutic duplication, or potential ADRs. Therefore, these three DURs, or variations developed based on them, can be used in a retrospective way to verify the quality of drug therapy at any health facility. They can also be used prospectively when incorporated into a computerized prescription or medical record system. Ideally, DURs should be combined with the bar-code technology for medication administration in inpatient facilities. DURs can verify that medications with anticholinergic activity are prescribed properly and can serve as a reminder to prescribing clinicians of the need to prescribe them carefully in patients with IDs. These two DURs (Appendices 2-3) are, therefore, a summary of how the implementation of the guideline for each specific compound would look in the real world.

2. Guideline for polypharmacy of drugs with anticholinergic activity

This guideline begins with an introduction on muscarinic receptors (Section 2.1.). It is followed by a section on the drugs with clinically relevant antimuscarinic activity (Section 2.2.). Next is a list with a table summarizing drugs with definitive or possible antimuscarinic activity (Section 2.3.). Possible ADRs associated with muscarinic blockade (Section 2.4.) are described; after that, three sections focus on the factors and situations that may potentiate the action of antimuscarinic drugs including pharmacokinetic DDIs (Section 2.5.), pharmacodynamic DDIs (Section 2.6.) and the patient's personal characteristics (Section 2.7.). Section 2.8 describes the DDI of antimuscarinic drugs with other drugs. Then three practical sections focus on definitions and documentation requirements including the definition of "polypharmacy of drugs with anticholinergic activity" (≥ 2 drugs with definitive antimuscarinic activity) (Section 2.9.), and the use of drug selection to avoid polypharmacy of drugs with anticholinergic activity (Section 2.10.). Section 2.11 considers "other situations with potential risk of polypharmacy with drugs with anticholinergic activity" by summarizing information from Sections 2.5., 2.6., and 2.7., thus not ignoring the risk of potential ADRs in unusual circumstances. Finally, a review of cholinergic rebound associated with sudden discontinuation of

potent antimuscarinic drugs is provided (Section 2.12.).

Appendix 1 describes the DUR's crucial practical aspects of this guideline; it includes a section on the polypharmacy of drugs with anticholinergic activity and a section on other situations with potential risk of polypharmacy with drugs with anticholinergic activity.

2.1. Introduction

This guideline focuses on the use of psychiatric and non-psychiatric drugs with anticholinergic activity in individuals with IDs. The term “drugs with anticholinergic activity” reflects the large number of drugs included in this category. These drugs may not be appropriately described as anticholinergic drugs, since the term “anticholinergic drugs” used in the literature refers to drugs that were originally developed for their anticholinergic activity. In this guideline, we include many drugs that were developed for other purposes but have displayed clinically relevant anticholinergic activity. Regarding the treatment of central nervous system (CNS) disorders, the so-called anticholinergic drugs were initially used in Parkinson's disease and then moved to psychiatry for treating EPS associated with antipsychotic treatment. Some of the first-generation psychiatric drugs, particularly some of the phenothiazines and the tricyclic antidepressants (TCAs), and some of the old non-psychiatric drugs (particularly the first generation of antihistamines) were soon identified as having clinically relevant anticholinergic properties.

2.1. Introduction to muscarinic receptors

This section focuses on the pharmacology of 1) muscarinic receptors, and 2) the related histaminic 1, H₁, receptors.

2.1.1. Muscarinic receptors

These receptors are called muscarinic because muscarine was found to be a selective agonist for them. Atropine was found to be an antagonist for the muscarinic receptors. Muscarinic receptors are found in three main areas of the body: 1) peripheral neurons, 2) central neurons, and 3) in the autocrine system (Brown & Taylor, 2006; Eglen, 2006). The peripheral neurons with muscarinic receptors include the autonomic effector cells innervated by the postganglionic parasympathic nerves, the autonomic ganglia cells and the adrenal medulla. Brain regions with a high density of muscarinic receptors include the hippocampus, the cortex and the thalamus. Muscarinic receptors are also present

in some cells, such as the endothelial cells of blood vessels that receive little or no cholinergic innervation. These muscarinic receptors are just beginning to be studied and appear to be part of the autocrine system (cells that secrete a hormone or chemical messenger that binds to receptors on the same cell). These receptors control 1) cell growth or proliferation (embryological development, oncogenesis, keratinocyte function), and 2) mediation of the release of chemical mediators from epithelial cells, which regulates contractility of smooth muscle in the vasculature, airways and urinary bladder (Eglen, 2006).

Study of the genes associated with the transcription of muscarinic receptors has led to the identification of 5 different receptors, M₁ to M₅. The clinical relevance of the different subtypes is unclear since it appears that tissues usually have more than one subtype of receptor (Brown & Taylor, 2006; de Leon, 2011). In summary, different subtypes of muscarinic receptors may not have much relevance for clinicians until the subject is better investigated.

2.1.2. H₁ receptors

The pharmacological literature clearly suggests that there may be some overlap between drugs causing muscarinic and those causing H₁ blockade (Rekker et al., 1971). All drugs with antimuscarinic properties tend to be sedating drugs and the sedating properties of these drugs are usually explained by H₁ blockade. All H₁ antagonists appear to have relevant antimuscarinic activity.

2.2. Drugs with clinically relevant antimuscarinic activity

These include anticholinergic drugs used as antiparkinsonian drugs, some drugs used for psychiatric indications (Tables 1-3) and some non-psychiatric (medical) drugs (Table 4). The most important psychiatric drugs are some antidepressants (Table 1) and some antipsychotics (Table 2). The most important non-psychiatric drugs are those developed as anticholinergic drugs including the most recently developed drugs for the treatment of overactive bladder and the antihistamines. Table 4 reviews other non-psychiatric drugs with questionable antimuscarinic activity.

2.2.1 Antiparkinsonian drugs

Benztropine, diphenhydramine, procyclidine, and trihexyphenidyl are anticholinergic compounds that have been used for their anti-parkinsonian properties. Their indications include:

Parkinson's disease (they were more frequently used before dopamine agonists were available), antipsychotic-induced parkinsonism, and the prevention and treatment of antipsychotic-induced acute dystonic reactions. Anticholinergics might decrease EPS by restoring the balance between dopamine and acetylcholine in the nigrostriatal system (Burgoyne et al., 2004). The few available *in vitro* studies (Coupet et al., 1985; Cusack et al., 1994; Fjalland et al., 1977; Friedel & Knauer, 1981; Miller & Hiley, 1974; Snyder et al., 1977; Syvälahti et al., 1987) clearly support that anticholinergic antiparkinsonians (benztropine, procyclidine and trihexyphenidyl) have great antimuscarinic potency.

2.2.2. Antidepressants

The majority of TCAs including amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, protryptiline, and trimipramine have clinically relevant antimuscarinic effects at clinical doses but in different degrees. Amitriptyline may be the most potent. Desipramine and other antidepressants related to TCAs, amoxapine and maprotiline probably have low antimuscarinic activity (Table 1, upper part). Two second-generation antidepressants, paroxetine and mirtazapine, may have mild antimuscarinic activity (Table 1, upper part); some articles postulate that other second-generation antidepressants may have activity, while most authors consider them as lacking antimuscarinic activity (Table 1, lower part). To simplify classification of antimuscarinic activity among antidepressants with clinically relevant activity, they can be divided into those with: 1) high potency: amitriptyline, clomipramine, and protryptiline; 2) moderate potency: doxepin, imipramine, nortriptyline, and trimipramine; and 3) low potency, which may be relevant only in high doses (possible activity): amoxapine, desimipramine, maprotiline, mirtazapine, and paroxetine. Other antidepressants less likely to have low antimuscarinic activity are listed in the lower part of Table 1.

2.2.3. Antipsychotics

Among first-generation antipsychotics, the low-potency phenothiazines, chlorpromazine and thioridazine are potent antimuscarinic drugs (de Leon et al, 1994a). Clozapine has potent antimuscarinic effects but, paradoxically, its use is frequently associated with hypersalivation. The muscarinic agonist properties of clozapine and/or its main metabolite (Davies et al., 2005) or its α receptor antagonist properties may explain hypersalivation during clozapine treatment. Some literature supports the theory that loxapine, olanzapine and quetiapine may have low antimuscarinic

activity, which may occasionally be clinically relevant (Table 2, upper part). In summary, antipsychotics with antimuscarinic activity can be divided into those with: 1) definitive antimuscarinic potency including chlorpromazine, clozapine and thioridazine; and 2) low potency that may be relevant only in high doses (possible activity), including loxapine, olanzapine, and quetiapine. Some articles postulate that other antipsychotics may have antimuscarinic activity, while most authors consider them as lacking antimuscarinic activity (Table 2, lower part).

2.2.4. Other anticholinergic drugs

They include antiemetics (meclizine, promethazine and prochlorperazine), drugs for peptic ulcer (hyoscyamine and propantheline), muscle relaxants (cyclobenzaprine, and orphenadrine), cyproheptadine, bronchodilators (tiotropium), antiarrhythmics (disopyramide), and drugs for dizziness (scopolamine) (Carnahan et al., 2006; Mintzer & Burns, 2000; Peters, 1989). Some anticholinergics are used as antispasmodic agents for their actions at the GI tract (dicyclomine) and/or at the bladder (see next section: 2.2.5.). Some anticholinergics, including homatropine, are used as ophthalmic agents to cause mydriasis but have very little or no systemic effects in normal circumstances. Ipratropium is a bronchodilator that has very little or no systemic effects in normal circumstances; it is included in the list of those with possible activity (Table 5, right side). Scopolamine and glycopyrrolate are anticholinergics used by anesthesiologists usually in the preoperative phase via the parenteral route to decrease salivation and excessive secretions in the respiratory tract secondary to vagal stimulation. A study adding drugs to serum and measuring SAA by RRA indicated that, as expected, atropine, dicyclomine and hyoscyamine have high antimuscarinic activity (Chew et al, 2008).

2.2.5. Treatment for overactive bladder

Darifenacin, fesoterodine, flavoxate, oxybutynin, oxybutynin transdermal system, solifenacin, tolterodine, and trospium are anticholinergic drugs used in the treatment of overactive bladder (Abrams & Andersson, 2007; MacDiarmid, 2007). Oxybutynin and tolterodine had relevant SAA by RRA (Chew et al., 2008). A clinical study on volunteers suggested that, for trospium, only extraordinarily high doses are associated with obvious antimuscarinic ADRs (Breuel et al., 1993).

2.2.6. Antihistamines

The first-generation oral antihistamines include brompheniramine, carbinoxamine, chlorpheniramine, clemastine, dimenhydrinate, diphenhydramine, and hydroxyzine) (Carnahan et al., 2004; Lehman & Blaiss, 2006; Peters, 1989; Rudolph et al., 2008). *In vitro* studies suggest that clemastine, cyproheptadine, dimenhydrinate, diphenhydramine, orphenadrine, and promethazine are more potent antimuscarinics (Cuscak et al., 1994; Fjalland et al., 1977; Kubo et al., 1987; Stanton et al. 1993), while carbinoxamine, chlorpheniramine, hydroxyzine and meclizine have lower muscarinic affinity (Cuscak et al., 1994; Kubo et al., 1987).

Most of the reviews on the second-generation antihistamines (Lehman & Blaiss, 2006; Meltzer, 2005), when discussing CNS ADRs focused on their sedative effects, are probably mediated by H₁ blockade more than by their antimuscarinic effects. As fexofenadine does not cross the blood-brain barrier, there is agreement that this would be the best oral antihistamine choice when trying to avoid sedation (Lehman & Blaiss, 2006; Meltzer, 2005). The second-generation oral antihistamines have low levels of ADRs in general; dry mouth is the most frequent of the antimuscarinic ADRs and is present in <10% of patients taking cetirizine, desloratidine, levocetirizine, and loratidine while it may be absent in fexofenadine (Lehman & Blaiss, 2006). Animal models agree that cetirizine and fexofenadine may not have antimuscarinic activity (Liu et al., 2005; 2006; Orzechowski et al., 2005) while indicating that loratidine and desloratidine may have some antimuscarinic activity (Cardelus et al., 1999; Liu et al., 2005; 2006; Orzechowski et al., 2005), but there are some negative results (Howell G 3rd et al., 2005). An SAA study with drugs added in different concentrations suggested that cetirizine and loratidine may have no relevant antimuscarinic activity measured by RRA (Chew et al., 2008). Thus, cetirizine, desloratidine, levocetirizine, and loratidine are considered as having only possible antimuscarinic activity (Table 5, right side).

2.3. List of drugs

Many drugs may have antimuscarinic activity. To facilitate their identification they are classified alphabetically (Table 5). The left side of Table 5 lists drugs with definitive antimuscarinic activity. The right side includes those that have possible activity. As an evidence-based approach is not possible, some arbitrariness was used to develop this table; a footnote supplies additional drugs that can be included in the table if one wants to be more lenient in the inclusion criteria. Tables 1 to 4

provide information on drugs with more questionable antimuscarinic activity.

2.4. ADRs

Drugs associated with antimuscarinic activity can cause peripheral ADRs and CNS ADRs.

2.4.1. *Peripheral ADRs*

These include decreased sweating that may contribute to hyperthermia and heat stroke, mydriasis, blurred vision, decreased lacrimation, decreased and thickened bronchial secretions, increased heart rate, dry mouth, decreased gastric acidity and delayed gastric emptying, decreased pancreatic secretion, decreased intestinal peristalsis that may cause constipation, and decreased bladder tone that may cause urinary retention (Mintzer & Burns, 2000; Peters, 1989). It is important to acknowledge that with some ADRs, such as blurred vision, tolerance to antimuscarinic effects may develop (Oshika, 1995).

2.4.2. *CNS ADRs*

These include memory deficits, sleep disturbances, more global cognitive deficits, or even delirium with or without hallucinations. To cause these CNS ADRs the antimuscarinic drugs must cross the blood-brain barrier.

2.5. *Potentiation of antimuscarinic activity by pharmacokinetic DDIs*

Pharmacology is a mechanistic science that allows predictions based on the mechanisms underlying pharmacological activity. Although it has not been systematically studied, indirect literature evidence clearly supports the concept that higher doses of drugs with antimuscarinic activity are more prone to cause antimuscarinic ADRs (de Leon, 2011). The fact that antimuscarinic ADRs are likely to be dose-related allows some pharmacological predictions. Obviously a dose increase of a drug with antimuscarinic activity in a patient should necessarily be associated with higher serum and brain concentrations as long as the drug crosses the blood-brain barrier. Pharmacokinetics predicts that decreased drug metabolism by an inhibitor is equivalent to dose increases, since decreased metabolism is associated with higher serum concentrations and is equivalent to giving higher doses in the absence of metabolic inhibition. Thus, if any drug with antimuscarinic activity is co-administered with a potent metabolism inhibitor, this would be equivalent to increasing drug levels and serum anticholinergic activity. The metabolism of old drugs with antimuscarinic activity has not been

systematically studied, but some information is available for some of these drugs.

2.5.1. *CYP2D6 drugs*

There is definitive agreement in the literature that some of these drugs with antimuscarinic activity are dependent on CYP2D6 for their metabolism, including phenothiazines (de Leon et al., 2006; Kirchheiner et al., 2004; Scordo & Spina, 2002; Zhou, 2009) and tolterodine (Zhou, 2009). Other drugs including benztropine (Armstrong & Schweitzer, 1997), chlorpheniramine (Zhou, 2009), darifenacin (Abrams & Andersson, 2007), diphenhydramine (de Leon & Nikoloff, 2008; Zhou, 2009), fesoterodine (Lacy et al., 2009), and promethazine (Lacy et al., 2009) are probably dependent on CYP2D6 for their metabolism. Thus, administering potent CYP2D6 inhibitors such as paroxetine and fluoxetine or moderate CYP2D6 inhibitors such as bupropion and duloxetine (Spina et al., 2008) may be associated with increased risk for muscarinic ADRs when taking any of the drugs mainly metabolized by CYP2D6. There is less ADR risk when CYP2D6 inhibitors are administered with CYP2D6 drugs that have only possible antimuscarinic activity, including loratidine (Zhou, 2009) and desloratidine (Zhou, 2009).

2.5.2. *CYP1A2 drugs*

Clozapine (de Leon et al., 2005; Spina & de Leon, 2007) and cyclobenzaprine (Lacy et al., 2009) depend on CYP1A2 for their metabolism. Powerful CYP1A2 inhibitors such as fluvoxamine (Diaz et al., 2008) and moderate CYP1A2 inhibitors such as ciprofloxacin, cimetidine, and high caffeine intake (de Leon et al., 2005) may be associated with increased risk for muscarinic ADRs when taking any CYP1A2 drugs. There is less ADR risk when CYP1A2 inhibitors are administered with CYP1A2 drugs that have only possible antimuscarinic activity, including olanzapine.

2.5.3. *CYP3A drugs*

Drugs with antimuscarinic activity dependent on CYP3A include disopyramide, fesoterodine, oxybutynin, and solifenacin (Abrams & Andersson, 2007; Lacy et al., 2009). Others partly metabolized by CYP3A include darifenacin (Abrams & Andersson, 2007) and tolterodine (Abrams & Andersson, 2007). Thus, co-prescription with clinically relevant CYP3A inhibitors (e.g., ketoconazole, itraconazole, fluconazole, erythromycin, fluoxetine, fluvoxamine, clarithromycin or diltiazem) may be associated with increased risk for muscarinic ADRs when taking any drug

metabolized by CYP3A. Obviously the co-prescription of any powerful CYP inducer (e.g., carbamazepine, phenytoin, phenobarbital or primidone) with any of these medications having clinically relevant antimuscarinic activity may decrease the potential of antimuscarinic ADRs by decreasing their serum levels.

2.5.4. TCAs

TCAs are complex drugs. TCAs are mainly metabolized by CYP2D6 (de Leon et al., 2006; Kirchheiner et al., 2004; Zhou et al., 2009). However, other CYP isoenzymes may have clinically relevant roles in some of them (Kirchheiner et al., 2004) and increase their levels. TCAs are narrow therapeutic index drugs; thus, whenever any potent CYP inhibitor is added, pay careful attention to increased risk for antimuscarinic activity and other ADRs.

2.6. *Potentiation of antimuscarinic activity by pharmacodynamic DDIs*

As muscarinic receptors act in multiple organs, pharmacodynamic DDIs can potentiate antimuscarinic ADRs using different mechanisms at a specific organ. Pharmacological mechanisms clinically relevant for DDIs include: 1) increased heart rate and sinus tachycardia risk, 2) decreased gastric motility and delayed gastric emptying, 3) decreased intestinal peristalsis with risk of constipation and even paralytic ileus, and 4) decreased sweating and heat stroke risk.

2.6.1. *Increased heart rate*

Sinus tachycardia can also be associated with stimulant and related drugs (amphetamines, methylphenidate, atomoxetine, and rarely with modafinil), and some calcium channel blockers from the dihydropyridine family (amlodipine, felodipine, isradipine, and nifedipine) (Hoffman, 2006). Thus, combining any of these drugs and drugs with antimuscarinic activity increases tachycardia risk. On rare occasions some of the antipsychotic drugs can cause orthostatic changes, particularly during the upward titration, and they can be associated with tachycardia. Some antipsychotics with no antimuscarinic activity (iloperidone, risperidone and ziprasidone) can be associated with orthostatic changes and secondary tachycardia. Therefore, the combination of medications with definitive antimuscarinic activity and iloperidone, risperidone or ziprasidone may require some vigilance during the antipsychotic titration.

2.6.2. *Decreased gastric motility*

An oral antidiabetic, pramlintide, can decrease gastric motility. Much caution should be used when combining pramlintide with drugs with potent antimuscarinic activity; they may have additive effects in delaying gastric emptying (Lacy et al., 2009).

2.6.3. Decreased intestinal peristalsis

Multiple medications can contribute to constipation by means of different mechanisms including antacids containing aluminum or calcium, calcium channel blockers, calcium supplements, cholestyramine and colestipol, clonidine, diuretics, iron supplements, levodopa, non-steroidal anti-inflammatory drugs (NSAIDs), opioids and vinca alkaloids (Arce et al., 2002; Bouras & Tangalos, 2009; Jacobs & Pamies, 2001; Spinzi, 2007). Thus, combining any of these drugs and drugs with antimuscarinic activity increases constipation risk.

2.6.4. Decreased sweating and heat stroke risk.

Antimuscarinic drugs can definitively cause anhydrosis by parasympathomimetically inhibiting sweat secretion, thus contributing to hyperthermia and heat stroke risk. There is more definitive risk if the patient is taking other drugs that may potentiate anticholinergic effects, including antipsychotics and carbon anhydrase inhibitors (acetazolamide, topiramate and zonisamide). Antipsychotics can interfere with heat regulation. Carbon anhydrase inhibitors can inhibit sweating and have also been associated with heat stroke (Nolla-Salas et al., 2007; Shimizu et al., 1997). The risk is clear when patients are exposed to heat and/or strenuous exercise (Martin-Latry et al., 2007; Stadnyk & Glezos, 1983). Fatal heat stroke occurs mainly in the elderly (Peters, 1989). The co-administration of drugs with antimuscarinic activity and exposure to hot weather or strenuous exercise should be accompanied by particular vigilance for hyperthermia and heat stroke.

2.7. Increased risk of antimuscarinic ADRs due to personal characteristics

Certain preexisting personal characteristics of the patient before starting antimuscarinic drugs may increase ADR risk when taking antimuscarinic drugs and are relative contraindications. They include 1) Sjogren syndrome, 2) preexisting tachycardia or patients in whom increased heart rate is not recommended, 3) preexisting constipation and/or decreased GI motility, 4) prone to urinary retention and/or preexisting benign prostate hyperplasia; 5) geriatric age and 6) dementia.

2.7.1. Sjogren syndrome

Antimuscarinic drugs are contraindicated in patients with dry mouth and/or dry eyes including conditions such as Sjogren syndrome.

2.7.2. Preexisting tachycardia or patients in whom increased heart rate is not recommended

Antimuscarinic drugs can cause tachycardia, and should be used cautiously in patients with tachycardia or in whom increased heart rate is not recommended.

2.7.3. Preexisting constipation and/or decreased GI motility

As antimuscarinic drugs can cause decreased GI motility, they should be used cautiously in patients with constipation and/or decreased GI motility.

2.7.4. Prone to urinary retention and/or preexisting benign prostate hyperplasia

Antimuscarinic drugs can interfere with detrusor muscle contraction; they should be used cautiously in patients prone to urinary retention and/or with benign prostate hyperplasia.

2.7.5. Geriatric patients

Geriatric patients are particularly prone to sedation, cognitive impairment, delirium or hallucinations when taking antimuscarinic medication. Although the effect of aging in muscarinic neurotransmission has not been well studied, elderly patients may be more sensitive to the blockade of cholinergic and histaminic receptors, and there may be decreased brain cholinergic activity with aging (Peters, 1989; Trifiro & Spina, 2011). Another factor that can contribute to antimuscarinic ADRs is that the blood-brain barrier may be more permeable in the elderly (Cancelli et al., 2009).

2.7.6. Demented patients

Neuropathological and brain imaging studies (Sunderland et al., 1987) show a decrease in brain muscarinic receptors in Alzheimer disease. Demented patients should not be treated with medications with antimuscarinic activity.

2.8. DDIs of antimuscarinic drugs with other drugs

Gastric emptying delays can cause pharmacokinetic DDI by changing the absorption of different drugs (Peters, 1989) but it is unknown whether this is clinically relevant or not. A pharmacodynamic DDI with acetylcholinesterase inhibitors is definitively clinically relevant.

2.8.1. Acetylcholinesterase inhibitors

These drugs (donepezil, galantamine, rivastigmine and tacrine) increase acetylcholine levels

in the synapse while antimuscarinic drugs interfere with acetylcholine binding to muscarinic receptors. It makes no pharmacological sense to combine acetylcholinesterase inhibitors with any drug with clinically relevant antimuscarinic activity (Carnahan et al., 2004). In conclusion, using drugs with antimuscarinic activity in demented patients taking acetylcholinesterase inhibitors is contraindicated because these drugs: 1) may decrease or eliminate the effect of the acetylcholinesterase inhibitors, and 2) may easily cause cognitive deficits in demented patients who are very sensitive to muscarinic blockade. Combining an acetylcholinesterase inhibitor and a drug with definitive antimuscarinic activity (see Table 5, left side) is contraindicated. If present, major justification with very careful documentation or a documented plan for discontinuation of the drug with definitive antimuscarinic activity or the acetylcholinesterase inhibitor is needed. The combination of an acetylcholinesterase inhibitor and a drug with possible antimuscarinic activity (see Table 5, right side) should be avoided. If present, justify with careful documentation.

2.9. Definition of polypharmacy of drugs with anticholinergic activity

Polypharmacy of drugs with anticholinergic activity is defined as taking two drugs with definitive antimuscarinic activity (see Table 5, left side). Although no studies support the use of this definition in individuals with ID, combining two drugs with definitive antimuscarinic activity may be clinically relevant and may even be associated with risk for cognitive impairment. If the anticholinergic medications are not for psychiatric purposes, the family medicine physician or a similar clinician can be responsible for this documentation. The physician assessment of any ID patient taking two of these drugs with definitive antimuscarinic activity will describe it as polypharmacy of drugs with anticholinergic activity. The patient will be more closely monitored for sedation and cognitive deficits, and the psychiatrist, the family medicine physician, or a similar clinician needs to comment on the risk and benefits of this type of polypharmacy. When a patient is taking one of these drugs with relevant antimuscarinic activity and a second one is added, the nursing assessment will include alarm at obvious cognitive impairment compared with cognition before initiating the second drug.

2.10. Preventing polypharmacy with anticholinergic drugs by means of drug selection

When a patient is taking a drug with relevant antimuscarinic activity and there is need for: 1)

a second-generation oral antihistamine, consider fexofenadine; or 2) treatment for overactive bladder, consider trospium.

2.10.1. Antihistamines with less potential for antimuscarinic ADRs

Most second-generation oral antihistamines (cetirizine, desloratidine, levocetirizine, and loratidine) may potentially cause sedation and slightly increase the risk of peripheral antimuscarinic ADRs such as dry mouth. In contrast, fexofenadine, as it does not cross the blood-brain barrier, appears free of sedating effects even at higher-than-therapeutic doses (Lehman & Blaiss, 2006). If an individual with ID is already taking a drug with definitive antimuscarinic activity and an oral antihistamine is needed, fexofenadine appears to be the best choice.

2.10.2. Treatment for overactive bladder with less potential for antimuscarinic ADRs

If an individual with ID is already taking a drug with definitive antimuscarinic activity and a drug for overactive bladder is needed, trospium appears to be the best choice since it does not cross the blood-brain barrier (Abrams & Andersson, 2007). However, trospium may contribute to ADRs by blocking peripheral muscarinic receptors. This should be discussed in the risk/benefit analysis when adding trospium to another medication with definitive antimuscarinic activity.

2.11. Other situations of potential risk for polypharmacy with medications with anticholinergic activity

Using a simple polypharmacy definition of drugs with anticholinergic activity by focusing only on patients taking two drugs with definitive antimuscarinic activity (Section 2.9) will facilitate the psychiatrist's documentation and his/her focus in cases with more obvious risk. This practical guideline has already indicated that other factors and situations may contribute to the risk of antimuscarinic ADRs in patients. These factors and situations have not been studied but are likely to be associated with lower risk of ADRs than that of taking two potent antimuscarinic drugs. To focus on all of these factors and situations and document them may be complicated for psychiatrists. This guideline, developed in facilities staffed by pharmacists, proposes that the pharmacist document how to lower the risks involved in polypharmacy with anticholinergic activity in the pharmacy section of the psychiatric assessments, focusing on DDI. If these guidelines are used by clinicians working in the community without pharmacy support, these clinicians will need to reconsider what level of

documentation is possible. The DURs may serve as a means of recollection.

In this guideline, the pharmacist is also responsible for reminding the psychiatrist or family medicine physician or similar clinician when any of these situations may have clinical relevance and/or are contributing to ADRs. These other situations of potential risk for polypharmacy with medications with anticholinergic activity that require pharmacist documentation include: 1) the combination of one drug from the list of those with definitive antimuscarinic activity (left side of Table 5) and one drug with possible antimuscarinic activity (right side of Table 5), 2) the presence of drug/s with anticholinergic activity having actions potentially increased by pharmacokinetic DDIs (see Section 2.5), 3) the presence of drug/s with anticholinergic activity but having actions potentially increased by a pharmacodynamic DDI (see Section 2.6.), or 4) the presence of drug/s with anticholinergic activity having actions potentially increased by a patient's personal characteristics (see Section 2.7.). Another situation requiring pharmacist documentation is the presence of drug/s with anticholinergic activity when the patient is taking acetylcholinesterase inhibitors (see section 2.8.).

2.12. Cholinergic rebound

Cholinergic rebound has been addressed in detail in prior guidelines and drug utilization reviews focused on clozapine (Sabaawi et al., 2006) and other antipsychotics with potent antimuscarinic activity. Sudden discontinuation of antimuscarinic drugs can be associated with cholinergic rebound manifested by nausea/vomiting, diarrhea, diaphoresis, restlessness and insomnia. The literature has described cholinergic rebound after abrupt discontinuation in patients taking TCAs (Dilsaver, 1990), phenothiazines and antiparkinsonians (Simpson et al., 1965) and clozapine (de Leon et al., 1994b). Cholinergic rebound can be treated with anticholinergic agents (de Leon et al., 1994b). According to Abrams & Andersson (2007), only oxybutinin has been associated with withdrawal symptoms among those antimuscarinic drugs used to treat overactive bladder. In summary, if any drugs with potent antimuscarinic activity (such as TCAs, phenothiazines, clozapine or oxybutinin) need to be abruptly discontinued due to serious ADRs, and symptoms of cholinergic rebound appear, the prescriber should consider the risk/benefits of adding an antiparkinsonian (de Leon et al., 1994b) for a few days and discontinuing it very slowly.

3. Benztropine guideline

This guideline follows the pattern of prior published guidelines (de Leon et al., 2009; Sabaawi et al., 2006). It begins with an introduction (Section 3.1.). Two sections then focus on indications for oral (Section 3.2.) and parenteral use (Section 3.3.). Next are sections for absolute (Section 3.4) and relative contraindications (Section 3.5.). A brief section on assessments during treatment (Section 3.6.) is followed by comprehensive sections on oral dosing in adults (Section 3.7.) and ADRs (Section 3.8.). Appendix 2 describes the DUR for oral benztropine, which summarizes the crucial aspects of the benztropine guideline. Appendix 3 summarizes the use of parenteral benztropine.

3.1. Introduction

Benztropine is an anticholinergic compound that exhibits anti-parkinsonian properties by blocking muscarinic receptors in the nigrostriatal system. Although the precise efficacy mechanism in Parkinson disease and in antipsychotic-induced EPS is not well known, anticholinergics appear to restore the disturbed balance between dopamine and acetylcholine in the nigrostriatal system (Burgoyne et al., 2004). There are few studies on benztropine pharmacokinetics, but CYP2D6 may be a metabolic pathway for benztropine (Lacy et al., 2009).

3.2. Indications for oral use

Benztropine was FDA-approved many years ago. Thus, the package inserts (Nexus Pharmaceuticals, Inc., 2009; Par Pharmaceuticals, Inc., 2005; Upsher-Smith Laboratories, Inc., 2002) generally describe benztropine as being indicated for adjunct use in all forms of parkinsonism and as useful in all antipsychotic-related EPS except for tardive dyskinesia (TD). Literature reviews (Boodhoo & Sandler, 1991; Burgoyne et al., 2004; Gelenberg, 1984; Mallet, 1989; Murphy & Stewart, 1979; Stanilla & Simpson, 2009) provided a more comprehensive list of benztropine indications. Care was taken to be precise in the specific indication and to provide alternatives.

At least one of the following clinical indications for oral benztropine should be present and documented in the chart prior to treatment:

3.2.1. Adjunctive treatment in Parkinson disease

Anticholinergics were introduced as the first treatment for Parkinson disease (Katzenschlager et al., 2003; Olanow et al., 2009). A few double-blind clinical trials indicate that anticholinergic drugs

are better than placebo in the symptomatic management of Parkinson disease (Katzenschlager et al., 2003). However, after levodopa was introduced in the 1960s, anticholinergics were no longer first-line treatments in Parkinson disease due to their associated cognitive deficits (Katzenschlager et al., 2003; Olanow et al., 2009). Anticholinergics are sometimes used in younger patients with Parkinson disease in whom resting tremor is the predominant symptom (Olanow et al., 2009). There is no published literature on the development of Parkinson disease in individuals with IDs. As individuals with IDs reach older age, they may receive the diagnosis of Parkinson disease; in our experience this diagnosis is being used by clinicians treating individuals with ID who have reached geriatric age. Individuals with ID may be particularly prone to cognitive impairment; therefore, this greater risk should be considered if an anticholinergic such as benztropine is considered for adjunctive treatment of Parkinson disease in an individual with ID.

3.2.2. Treatment of reversible antipsychotic-induced EPS

There are 3 major reversible antipsychotic-induced EPS: acute dystonic reactions, parkinsonism and akathisia (Stanilla & Simpson, 2009). Hypersalivation can be one of the parkinsonian symptoms but it can have other etiologies; thus, it is listed separately in Section 3.2.5. Second-generation antipsychotics appear to be associated with lower EPS risk, but naturalistic studies in the clinical environment indicate that their use with co-prescribed anticholinergics has decreased but has not been eliminated. These studies indicate more frequent anticholinergic co-prescription when using risperidone than other second-generation antipsychotics (Hong & Bishop, 2010; Yang et al., 2007), which fits in with risperidone's poorer EPS profile in a meta-analysis of antipsychotic controlled trials (Jayaram et al., 2006; Leucht et al., 1999).

A. Acute dystonic reactions. The studies of first-generation antipsychotics clearly indicate that acute dystonic reactions usually respond well to anticholinergic drugs. The second-generation antipsychotics rarely induce acute dystonic reactions and there are no treatment studies, but it is assumed that acute dystonic reactions are short-lived and do not tend to recur (Raja & Azzoni, 2001).

B. Parkinsonism. Antipsychotic-induced parkinsonian typically manifests with parkinsonian tremor, stiffness and/or bradykinesia. Treatment alternatives to the use of anticholinergics, such as benztropine, include decreasing the antipsychotic dosage or switching to an antipsychotic with less

risk of parkinsonian ADRs (Stanilla & Simpson, 2009). Rabbit syndrome is a parkinsonian orofacial tremor which occurs after prolonged antipsychotic use; it usually responds to anticholinergic medication (Catena et al., 2007).

C. Akathisia. Anticholinergic medication such as benztropine may be the first choice when akathisia is associated with other reversible EPS, but in other akathisia situations, anticholinergic medications may be a second or third choice (Labbate et al., 2010).

3.2.3. *Prophylaxis of acute dystonic reactions*

When first-generation antipsychotics were the only antipsychotic drugs available, benztropine and other anticholinergics were used as prophylaxis for patients with a history of acute dystonic reactions or some other high risk, such as young males started on high doses of haloperidol (or other high potency agents). Recommended doses were 1-4 mg/day (Stanilla & Simpson, 2009) or 2 mg twice a day (Labbate et al., 2010). Naturalistic studies (Spina et al., 1993) and controlled studies (Goff et al., 1991) indicated that with the haloperidol doses used in those times, anticholinergic treatment decreased but did not completely eliminate the risk of acute dystonic reaction. Due to the rarity of acute dystonic reactions on second-generation antipsychotics, anticholinergic prophylaxis probably is rarely needed when using second-generation antipsychotics in an average patient. However, patients with history of acute dystonic reactions may not be average patients. A recent double-blind prospective study in Chinese patients with history of antipsychotic-induced acute dystonic reactions (or at least moderate parkinsonism) found that, when patients were randomized to risperidone, 40% needed anticholinergics; however, when they were randomized to olanzapine, only 10% needed them (Chan et al., 2010). This controlled study suggests that risperidone should be avoided in patients with history of acute dystonic reactions or EPS intolerance, and a different second-generation antipsychotic (e.g., aripiprazole, olanzapine, quetiapine or ziprasidone) should be prescribed. Data from second-generation antipsychotic intoxications suggests that quetiapine may be the least likely of these antipsychotics to cause acute dystonic reactions (Ciranni et al., 2009).

3.2.4. *Primary or tardive dystonia*

The literature reports that both primary dystonia (Duvoisin, 1983) and tardive dystonia (Akiyama, 1999; Stanilla & Simpson, 2009) may respond to high doses of anticholinergics. For this

indication, the chart should note that an expert with experience in this area has been consulted and has indicated the use of high anticholinergic doses after considering other treatments.

3.2.5. Sialorrhea

There are multiples causes of sialorrhea including those associated with anatomical abnormalities, difficulties in swallowing and hypersalivation (increased saliva production) (Boyce & Bakheet, 2005; Nunn, 2000; Potulska & Friedman, 2005; Tscheng, 2002). In individuals with ID, chronic sialorrhea can be secondary to anatomical defects (e.g., macroglossia in Down syndrome) or to difficulties in swallowing associated with cerebral palsy. In these cases, an expert in the area should be consulted (Nunn, 2000; Potulska & Friedman, 2005) to consider other treatments, including botulinum toxin injections (Potulska & Friedman, 2005; Tscheng, 2002), before considering chronic treatment with oral anticholinergics such as benztropine (Camp-Bruno et al., 1989). Of more interest for this guideline is the treatment of drug-induced sialorrhea. Clozapine is the antipsychotic that most frequently causes hypersalivation (Sabaawi et al., 2006). The muscarinic agonist properties of clozapine and/or its main metabolite (Davies et al., 2005) or its α_2 antagonist properties may explain hypersalivation during clozapine treatment. A recent review reported that clozapine increases salivation during sleep and at rest and decreases it during meals (Ekström et al., 2010). There are no definitive studies to recommend the best treatment for clozapine-induced sialorrhea (Sockalingam et al., 2007; Syed et al., 2008). However, there are some recent double-blind studies: 1) of glycopyrrolate versus biperiden showing positive results from both drugs with a better ADR profile in glycopyrrolate (Liang et al., 2010); 2) of botulinum toxin by injections versus placebo, with positive results for botulinum toxin (Steinlechner et al., 2010), and 3) of ipatropium versus placebo, with negative results for ipatropium (Sockalingam et al., 2009). Case reports indicate that oral anticholinergics such as benztropine may be effective for treating clozapine-induced hypersalivation (Rogers & Shramko, 2000). Case reports also indicate that other alternatives with less risk of cognitive impairment than benztropine may be effective including: 1) botulinum toxin injections (Kahl et al., 2004); 2) anticholinergics with lower brain entrance than benztropine: atropine eye drops administered intraorally (Antonello & Tessier, 1999), glycopyrrolate (Robb et al., 2008), ipatropium sprays (Calderon et al., 2000; Tessier & Antonello, 2001), and scopolamine patches (Gaftanyuk &

Trestman, 2004); or 3) α_2 agonists clonidine (Grabowski, 1992; Praharaj et al., 2005) and guanfacine (Webber et al., 2004).

3.2.6. Other uses less frequently described in the literature

These require an explanatory note in the chart justifying the use of benztropine. The treatment of antidepressant-induced sweating is an example of an infrequent use of benztropine (Marcy & Britton, 2005).

3.3. Indications for parenteral use

Benzotropine can be administered intramuscularly (IM) or intravenously (IV). At least one of the following clinical indications is present for short acute or stat use of parenteral benztropine:

3.3.1. Antipsychotic-induced acute dystonic reactions or any other form of severe antipsychotic-induced EPS

Most times parenteral benztropine is administered via the IM route. Recommended doses for acute dystonic reactions in adults are 1-2 mg (Lacy et al., 2009) or 2 mg (Stanilla & Simpson, 2009). The dose can be repeated in 30 minutes if recovery is incomplete (Stanilla & Simpson, 2009). Parenteral benztropine may take less time to resolve acute dystonic reactions than parenteral diphenhydramine (Lee et al., 1979). If parenteral benztropine is effective, it is important to consider oral benztropine to avoid relapses after the rapid elimination of the parenterally-administered drug. An oral dose of 2 mg bid for 2 weeks is recommended. Even if the antipsychotic is discontinued, the oral benztropine should be continued for 2-3 days (Labbate et al., 2010). Currently there is no information on whether acute dystonic reaction induced by second-generation antipsychotics may require oral benztropine to avoid relapses after IM benztropine; however, clinicians are encouraged to use it, or at least consider it and document the risk-benefit in the chart. In special circumstances such as severe acute dystonic reactions including laryngeal dystonia, more aggressive treatment should be used including: the IV route and 4 mg dose repeated in 10 minutes (Labbate et al., 2010). If this is insufficient, a slow IV administration of 1-2 mg of lorazepam can also be added (Labbate et al., 2010).

3.3.2. Antipsychotic-induced EPS prophylaxis

IM benztropine should be co-administered with IM injections of high potency first-generation

antipsychotics for prophylaxis of reversible antipsychotic-induced EPS. These injections include normal and long-acting antipsychotic formulations. Prophylaxis is particularly important in highly vulnerable patients, especially for those with a history of acute dystonic reactions. Doses of benztropine 1-2 mg IM appear reasonable in these cases but prior history can be used to guide dosing. A meta-analysis of second-generation IM trials indicates that administering IM haloperidol plus an IM antihistaminic-anticholinergic drug (promethazine) was not associated with acute dystonias, and its profile is as good as the IM second-generation antipsychotics (Satterthwaite et al., 2008).

3.4. Absolute contraindications for use

Absolute contraindications are 1) hypersensitivity to benztropine or any other compound of the formulation, and 2) any conditions in which antimuscarinic medications are contraindicated. The latter include pyloric or duodenal obstruction, bladder neck obstruction, achalasia, myasthenia gravis (Lacy et al., 2009) or narrow-angle glaucoma (Oshika, 1995).

3.5. Relative contraindications for use (unless benefit outweighs risk with documentation)

3.5.1. Patient personal characteristics present before starting benztropine

Some patient personal characteristics may increase ADR risk when taking antimuscarinic drugs. They include:

- A. Sjogren syndrome. Antimuscarinic drugs are not indicated in patients with dry mouth and/or dry eyes including conditions such as Sjogren syndrome.
- B. Preexisting tachycardia or patients in whom increased heart rate is not recommended. Antimuscarinic drugs can cause tachycardia, and should be used cautiously in patients with tachycardia or in whom increased heart rate is not recommended.
- C. Preexisting constipation and/or decreased GI motility. As antimuscarinic drugs can cause decreased GI motility, they should be used cautiously in patients with constipation and/or decreased GI motility.
- D. Prone to urinary retention and/or preexisting benign prostate hyperplasia. Antimuscarinic drugs can interfere with detrusor muscle contraction; they should be used cautiously in patients prone to urinary retention and/or benign prostate hyperplasia.
- E. Geriatric patients. Geriatric patients (≥ 65 years old) are particularly prone to sedation, cognitive

impairment, delirium or hallucinations when taking antimuscarinic medication (see Section 2.7.5.).

F. Demented patients should not be treated with medications with antimuscarinic activity due to the high risk of impairing their cognition (see Section 2.7.6.).

G. Presence of TD. TD does not usually respond to anticholinergic medication. Short-term challenges with anticholinergics are associated with worsening of dyskinetic movements (Gardos et al., 1984). Some case reports suggest improvement or disappearance of TD when anticholinergics were discontinued, despite staying on the antipsychotics (Yassa, 1985). Some evidence exists that long-term use of anticholinergics may increase TD risk (American Psychiatric Association Task Force on Tardive Dyskinesia, 1992; Labbate et al., 2010). Anticholinergic treatment is frequently associated with vulnerability to reversible EPS (American Psychiatric Association Task Force on Tardive Dyskinesia, 1992; Tenback et al., 2009), but it is unclear whether anticholinergic treatment directly increases TD risk, or is merely an epiphenomenon of the association between higher TD vulnerability of patients developing reversible EPS. In cross-sectional studies, the association of anticholinergic treatment with TD can be detected after correcting for other factors in patients with severe mental illness (de Leon, 2007) or adults with ID (Wszola et al., 2001). Although it cannot be ruled out that anticholinergic drugs may merely exacerbate or uncover movements rather than contribute to TD risk, the chart of a patient with TD should indicate that the benefit of benztropine outweighs the risk of worsening the dyskinetic movements.

3.5.2. Intake of drugs that may have pharmacodynamic DDIs which can potentiate benztropine

Documentation of how benefit outweighs risk is needed when patients are taking drugs that:

A. Increase heart rate. Sinus tachycardia can also be associated with stimulant and related drugs (amphetamines, methylphenidate, atomoxetine, and rarely with modafinil), and some calcium channel blockers from the dihydropyridine family (amlodipine, felodipine, isradipine, and nifedipine) (Hoffman, 2006). Thus, combining any of these drugs with drugs with antimuscarinic activity increases tachycardia risk.

B. Decrease gastric motility. An oral antidiabetic, pramlintide, can decrease gastric motility. Much caution should be used when combining pramlintide with drugs with potent antimuscarinic activity; they may have additive effects in delaying gastric emptying (Lacy et al., 2009).

C. Increase risk of constipation. Multiple medications can contribute to constipation through different mechanisms including antacids containing aluminum or calcium, calcium channel blockers, calcium supplements, cholestyramine and colestipol, clonidine, diuretics, iron supplements, levodopa, NSAIDs, opioids and vinca alkaloids (Arce et al., 2002; Bouras & Tangalos, 2009; Jacobs & Pamies, 2001; Spinzi, 2007). Thus, combining any of these drugs with drugs with antimuscarinic activity increases the risk of constipation.

D. Contribute to heat stroke risk. Benztropine, as with other anticholinergics, can definitively cause anhydrosis by parasympathomimetically inhibiting sweat secretion, thus contributing to hyperthermia and heat stroke risk. There is more definitive risk if the patient is taking other drugs that may potentiate anticholinergic effects, including antipsychotics and carbon anhydrase inhibitors (acetazolamide, topiramate and zonisamide). Antipsychotics can interfere with heat regulation. Carbon anhydrase inhibitors can inhibit sweating and have also been associated with heat stroke (Nolla-Salas et al., 2007; Shimizu et al., 1997). The risk is clear when patients are exposed to heat and/or strenuous exercise (Martin-Latry et al., 2007; Stadnyk & Glezos, 1983). Fatal heat stroke occurs mainly in the elderly (Peters, 1989). The co-administration of drugs with antimuscarinic activity and exposure to hot weather or strenuous exercise should be accompanied by particular vigilance for hyperthermia and heat stroke.

3.5.3. Benztropine's pharmacodynamic effects in specific drug combinations

Benztropine should not be combined with:

A. Anticholinergic drugs used as antiparkinsonians. Biperiden, diphenhydramine, procyclidine, and trihexyphenidyl are anticholinergic compounds that have been used for their anti-parkinsonian properties; there is no good pharmacological reason to use them with benztropine unless one is switching to or from benztropine.

B. Acetylcholinesterase inhibitors. These drugs (donepezil, galantamine, rivastigmine and tacrine) increase synaptic acetylcholine levels, while antimuscarinic drugs interfere with acetylcholine binding to muscarinic receptors. Thus the co-prescription of these drugs is not appropriate (Carnahan et al., 2004); it makes no pharmacological sense to combine acetylcholinesterase inhibitors with any drug with clinically relevant antimuscarinic activity.

3.6. Assessment during treatment

There is no need for initial or follow-up workups for benztropine.

3.6.1. Warning signs and symptoms for daily caretakers

The following may occur: 1) excessive sedation; 2) memory, sleep or cognitive disturbances; 3) blurred vision, increased heart rate, dry mouth, or constipation; or 4) decreased sweating with risk of hyperthermia.

3.7. Oral dosing in adults

3.7.1. Doses and maximum recommended dosage

Benztropine oral dose varies when used for treatment vs. prophylaxis.

A. Treatment of antipsychotic-induced EPS. The recommended oral dose for adults is 1-4 mg administered 1-2 times a day (Lacy et al., 2009). There is no clearly agreed-upon maximum recommended daily dose in the literature; doses up to 8 mg/day have been described (Stanilla & Simpson, 2009). Thus, any dose > 8 mg/day needs justification in the chart with a very thorough discussion validating the usage of higher doses and verifying that no ADRs are present.

B. Prophylaxis of antipsychotic-induced EPS. Benztropine prophylaxis may be used in patients started on high potency first-generation antipsychotics. Stanilla & Simpson (2009) recommend 1-4 mg/day. Any dose > 4 mg/day needs chart justification with a very thorough discussion validating the usage of higher doses and verifying the absence of ADRs. In patients with EPS history, if benztropine prophylaxis is used when starting a second-generation antipsychotic, the chart should discuss why another second-generation antipsychotic with less EPS risk (e.g., quetiapine) was not used.

3.7.2. Dosage modification associated with DDIs

Unfortunately, benztropine DDIs have never been systematically studied. Benztropine acts mainly by blocking muscarinic receptors. Other possible benztropine actions include blocking antihistaminic receptors, which may explain its sedating properties. It is also believed that benztropine may inhibit the dopamine transporter (Kulakarni et al., 2007; Lacy et al., 2009; Modell et al., 1989). Regarding benztropine pharmacokinetics, very few studies measure levels (Jindal et al., 1981; Selinger et al., 1989) or explore metabolites (He et al., 1993; Rosano et al., 1994). According to Lacy et al. (2009), benztropine is partly metabolized by CYP2D6.

A. Pharmacokinetic DDIs. Caution should be used when combining benztropine with potent (fluoxetine and paroxetine) or moderate (duloxetine, or bupropion) CYP2D6 inhibitors (Spina et al., 2008), since cases of delirium have been associated with benztropine level increases during treatment with paroxetine (Armstrong & Schweitzer, 1997; Roth et al., 1994). Other CYP inhibitors might possibly increase benztropine, since a delirium case was associated with high doses of sertraline, which might cause CYP2D6 inhibition (Byerly et al., 1996) and memory and attention impairment (Daniel et al., 1994) with fluvoxamine, a mild CYP2D6 inhibitor (Spina et al., 2008).

B. Pharmacodynamic DDIs. Carefully monitor for ADRs when other drugs which can cause pharmacodynamic DDIs are administered.

B.1. Benztropine may have additive sedative effects when combined with other sedating drugs, including anticonvulsants, antihistamines, benzodiazepines, opioids, some antidepressants and some antipsychotics.

B.2. Similarly, benztropine may have additive antimuscarinic effects when combined with other antimuscarinic drugs. Many drugs may have antimuscarinic activity (see Table 1), but there is definitive information that clinically relevant antimuscarinic activity is present for some antidepressants (amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine), some antipsychotics (chlorpromazine, clozapine, and thioridazine), some antiemetics (meclizine, promethazine and prochlorperazine), some drugs for peptic ulcer (hyoscyamine and propantheline), some muscle relaxants (cyclobenzaprine, and orphenadrine), cyproheptadine, some bronchodilators (tiotropium), some antiarrhythmics (disopyramide), some drugs for dizziness (scopolamine), drugs for overactive bladders (darifenacin, fesoterodine, flavoxate, oxybutynin, oxybutynin transdermal system, solifenacin, tolterodine, and trospium), and some first-generation oral antihistamines (clemastine, dimenhydrinate, and diphenhydramine). Due to potentially increased risk for cognitive impairment and peripheral antimuscarinic ADRs, much caution should be used when combining benztropine with any of these drugs with antimuscarinic activity. Moreover, the patient would meet criteria for Polypharmacy of Drugs with Anticholinergic Activity (see Section 2.9.).

B.3. Lower risks are present for other drugs with possible antimuscarinic activity (see Polypharmacy Guideline for Drugs with Anticholinergic Activity, Table 1), including some antidepressants

(amoxapine, desipramine, maprotiline, mirtazapine, and paroxetine), some antipsychotics (loxapine, olanzapine, and quetiapine), ipratropium, some first-generation antihistamines (brompheniramine, carbinoxamine, chlorpheniramine, and hydroxyzine), some second-generation oral antihistamines (cetirizine, desloratidine, levocetirizine, and loratidine), some H₂ antagonists (cimetidine and ranitidine) and temazepam. Due to potential added cognitive impairment and peripheral antimuscarinic ADRs, much caution should be used when combining benztropine with any of these drugs with possible antimuscarinic activity. Moreover, the patient would meet criteria for Potential Risk of Polypharmacy of Drugs with Drugs with Anticholinergic Activity (see Section 2.9.).

B.4. Other drugs that can cause tachycardia include stimulant and related drugs (amphetamines, methylphenidate, atomoxetine, and rarely with modafinil), and some calcium channel blockers (amlodipine, felodipine, isradipine, and nifedipine) (Hoffman, 2006). Thus, combining any of these drugs with drugs with antimuscarinic activity increases tachycardia risk. Rarely, some of the antipsychotic drugs can cause orthostatic changes, particularly during upward titration, which can be associated with tachycardia. Some antipsychotics with no antimuscarinic activity (iloperidone, risperidone and ziprasidone) can be associated with orthostatic changes and secondary tachycardia. Thus combining medications with definitive antimuscarinic activity and iloperidone, risperidone or ziprasidone may require some vigilance during the antipsychotic titration.

B.5. Pramlintide, an oral antidiabetic, can decrease gastric motility. Caution should be used when combining pramlintide with benztropine due to their additive effects in delaying gastric emptying.

B.6. Medications that can contribute to constipation include antacids containing aluminum or calcium, calcium channel blockers, calcium supplements, cholestyramine and colestipol, clonidine, diuretics, iron supplements, levodopa, NSAIDs, opioids and vinca alkaloids (see Section 3.5.2.C.). Combining any of these drugs with drugs with antimuscarinic activity increases constipation and ileus risk.

B.7. Antimuscarinic drugs can definitively cause anhydrosis by parasympathomimetically inhibiting sweat secretion, thus contributing to hyperthermia and heat stroke risk. There is more risk if the patient is taking other drugs that may potentiate antimuscarinic effects, including antipsychotics or carbon anhydrase inhibitors (acetazolamide, topiramate and zonisamide), exposure to heat and/or strenuous exercise and geriatric age (≥ 65 years).

3.7.3. *Dosing modifications of other drugs*

Benztropine is unlikely to cause pharmacokinetic DDIs and does not appear to behave as an inhibitor or inducer. Pharmacodynamic DDIs are described in the section above. As indicated in the relative contraindication section (see Section 3.5.3.), if benztropine is added, other anticholinergics used for their antiparkinsonian activity or acetylcholinesterase inhibitors should be discontinued.

3.7.4. *Dosing modifications associated with personal characteristics*

A. Lower benztropine dosages are recommended for geriatric patients. Labbate et al. (2010) recommends 1 mg bid. Thus, any dose > 2 mg/day needs justification in the chart of patients aged \geq 65 years with a very thorough discussion validating the use of higher doses and verifying that no ADRs are present.

B. As there are no studies in patients with hepatic or renal impairment, lower doses and caution are recommended.

3.7.5. *Discontinuation*

A. Treating reversible EPS. Benztropine should be tapered off slowly over weeks or months (Stanilla & Simpson, 2009) when possible (unless precluded for medical reasons) to minimize the potential of cholinergic rebound signs (Stanilla & Simpson, 2009) and the relapse of antipsychotic-induced EPS. Periodic attempts should be made to wean patients off anticholinergics when taking benztropine chronically for any reversible EPS in order to avoid increasing the risk of TD (Labbate et al., 2010; Stanilla & Simpson, 2009); these attempts should be reviewed and documented annually.

B. Preventing reversible EPS. When benztropine is used to prevent acute dystonic reactions, Stanilla & Simpson (2009) recommend weaning the dose slowly over 10 days while watching for the development of parkinsonism or akathisia.

3.8. *ADRs*

3.8.1. *Common ADRs*

This guideline assumes that ADRs explained by antihistaminic and antimuscarinic properties are common and probably dose-dependent, although they have never been systematically studied.

A. ADRs associated with antihistaminic blockade in the brain. Benztropine's H₁ receptor blockade probably explains its sedating properties. Patients must be cautioned about performing tasks that

require mental alertness (e.g., operating machines) until they are familiar with benztropine's effects (Lacy et al., 2009).

B. ADRs associated with brain antimuscarinic blockade including memory deficits, sleep disturbances, more global cognitive deficits, or even delirium with or without hallucinations. Antimuscarinic drugs are a frequent cause of delirium in the elderly (Mintzer & Burns, 2000; Peters, 1989).

C. ADRs associated with peripheral antimuscarinic blockade including decreased sweating that may contribute to hyperthermia and heat stroke; mydriasis; blurred vision; decreased lacrimation; decreased and thickened bronchial secretions; increased heart rate; dry mouth; nasal dryness; decreased gastric acidity and delayed gastric emptying; decreased pancreatic secretion; decreased intestinal peristalsis that may cause constipation, or even ileus; and decreased bladder tone that may cause urinary retention (Lacy et al., 2009; Mintzer & Burns, 2000; Peters, 1989). It is important to acknowledge that tolerance to some ADRs, such as blurred vision, may develop (Oshika, 1995).

3.8.2. Relatively uncommon ADRs

A. Skin rash. In a large sample, a macular rash on arms and legs was present in 1% of the patients (Doshay, 1956).

B. Anticholinergics including benztropine can be abused, but trihexyphenidyl may have the highest abuse potential (Buhrich et al., 2000; Stanilla & Simpson, 2009). Benztropine and other anticholinergics inhibit the dopamine transporter but it is not known if this contributes to their abuse potential or not; benztropine lacks cocaine-like behavioral effects and fails to potentiate the effects of cocaine (Kulkarni et al., 2006; Modell et al., 1989).

3.8.3. Potentially lethal ADRs.

A. A potentially lethal ADR is hyperthermia and/or heat stroke (Stadnyk & Glezos, 1983). Lethal cases of heat stroke combining antipsychotics and benztropine continue to be described in the literature (Kao et al., 2007).

4. Summary

These guidelines review the medications with anticholinergic activity in the US and focus on benztropine as an example of an antiparkinsonian drug. These practical guidelines are focused on

individuals with ID but we are not aware of similar guidelines in other neuropsychiatric populations. For these individuals, there is no information on implementing an evidence-based approach. Our limited knowledge of the pharmacokinetic and pharmacodynamic mechanisms of these drugs found in other neuropsychiatric disorders is used to try to develop a personalized medicine approach, which provides recommendations on the use of these drugs. These guidelines are pragmatic in that they were developed using prescribing information and a review of the available literature on other neuropsychiatric disorders.

In the absence of consensus guidelines and well-controlled comparison trials, we are presenting a set of guidelines to ensure proper utilization of each of these compounds in individuals with IDs. Section 2 focuses on all medications with anticholinergic activity. It describes the pharmacology of muscarinic receptors and of these drugs and provides a list of drugs with definitive or possible antimuscarinic activity. Three practical sections focus on the definition and documentation requirements including the definition of “polypharmacy of drugs with anticholinergic activity”, the use of drug selection to avoid polypharmacy of drugs with anticholinergic activity, and other situations with potential risk of polypharmacy with drugs with anticholinergic activity. Section 3 focuses on benztropine with its indications, contraindications, personalized dosing and ADRs.

Appendix 1 describes the DUR which contains the crucial practical aspects of the guideline, including all medications with anticholinergic activity. Included are a section on polypharmacy of drugs with anticholinergic activity and a section on other situations with potential risk of polypharmacy with drugs with anticholinergic activity. Appendix 2 describes the DUR for oral benztropine, which summarizes the crucial aspects of the benztropine guideline. Appendix 3 summarizes the use of parenteral benztropine.

Some of the statements comparing different compounds are admittedly arbitrary but are intended to establish a framework for clinicians. This framework is not intended to replace but to augment individual judgment and clinical expertise. Moreover, the field continues to evolve and emerging literature may become available following the development of these guidelines in the fall of 2010. The procedures contained in these guidelines may not fully account for all of the possible risks of treatment in this population because of the limited studies available; thus, there will be a need to

periodically update this guide as new knowledge becomes available. Nevertheless, we believe that these guidelines will be a useful resource for clinicians who treat seizures and/or challenging behaviors in adult individuals with IDs. In closing, it may be appropriate to remember the wisdom of Naylor (1995), “Clinical medicine seems to consist of a few things we know, a few things we think we know (but probably don’t), and lots of things we don’t know at all.” Unfortunately when treating adult individuals with ID, our ignorance is greater than when treating the average medical patient.

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No commercial organizations had any role in the writing of this paper for publication. Dr. de Leon personally develops his presentations for lecturing, has never lectured using any pharmaceutical or pharmacogenetic company presentation, and has never been a consultant for pharmacogenetic or pharmaceutical companies. In the past, Dr. de Leon has received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007); from Roche Molecular Systems, Inc. (ended in 2007); and, in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010). He has been on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). Roche Molecular Systems supported one of his educational presentations that was published in a peer-reviewed journal (2005). His lectures have been supported once by Sandoz (1997), twice by Lundbeck (1999 and 1999), twice by Pfizer (2001 and 2001), three times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and seven times by Roche Molecular Systems, Inc. (once in 2005 and six times in 2006).

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Table 1. Antidepressants with low or questionable antimuscarinic activity

ANTIDEPRESSANTS WITH LOW ANTIMUSCARINIC ACTIVITY	
-Amoxapine.	In vitro studies (Coupet et al., 1985; Davies et al., 2005; El-Fakahany & Richelson, 1983) indicate that amoxapine has low antimuscarinic activity and they agree on the low clinical risk for ADRs typically associated with antimuscarinic effects (Richelson, 2003).
-Desipramine.	In vitro studies (El-Fakahany & Richelson, 1983; Golds et al., 1980; Owens et al., 1997; Richelson & Divinetz-Romero, 1977; Snyder & Yamamura, 1977; Tollefson & Senogles, 1983) indicate desipramine has low antimuscarinic activity. Open clinical studies (Peterson et al., 1978; Szabadi et al., 1980) and a single dose study in volunteers under double-blind conditions (Blackwell et al., 1978) demonstrated mild antimuscarinic effects. Another volunteer study under double-blind conditions (Arnold et al., 1981) was not able to demonstrate its antimuscarinic effects.
-Maprotiline.	In vitro studies (El-Fakahany & Richelson, 1983; Golds et al., 1980; Tollefson & Senogles, 1983) indicate that maprotiline has low affinity for muscarinic receptors and mild ADRs were demonstrated in a volunteer study under double-blind conditions (Carlini et al., 1985).
-Mirtazapine.	In vitro studies (de Boer et al., 1988; Nutt, 1997); SAA by RRA (Chew et al., 2008); ADR case reports (Bailer et al., 2000); clinical studies (Montgomery et al., 1998; Smith et al., 1990); or reviews of clinical studies (Holm & Markham, 1999; Montgomery, 1995; Nutt, 1997) indicate that <u>mirtazapine may have very low antimuscarinic activity, much lower than most TCAs.</u>
-Paroxetine.	In vitro studies (Cusack et al., 1994; Owens et al., 1997; Thomas et al., 1987); animal models (Fujishiro et al., 2002); SSA by RRA (Chew et al., 2008; Pollock et al., 1998) and ADR case reports (Arima et al., 2005) indicate that paroxetine has low antimuscarinic activity that can <u>occasionally be clinically relevant.</u>
ANTIDEPRESSANTS WITH WITH QUESTIONABLE ANTIMUSCARINIC ACTIVITY	
-Citalopram:	Positive data: Mild SAA by RRA (Chew et al., 2008). Negative data: In vitro studies (Richelson & Nelson, 1984) and review article (Richelson, 2003).
-Escitalopram:	Positive data: Mild SAA by RRA (Chew et al., 2008).
-Fluoxetine:	Positive data: Mild SAA by RRA (Chew et al., 2008). Negative data: Irrelevant activity in vitro studies (Owens et al., 1997; Stanton et al., 1993) and review (Richelson, 2003).
-Sertraline:	Positive data: Mild activity in in vitro studies (Cusack et al., 1994; Owens et al., 1997; Stanton et al., 1993) and reviews (Carnaham et al., 2006; Richelson, 2003). Negative data: SAA by RRA (Chew et al., 2008).
-Trazadone:	Positive data: According to review (Rudolph et al., 2008). Negative data: In vitro studies (Cusack et al., 1994; Owens et al., 1997; Stanton et al., 1993; Tollefson & Senogles, 1983) and SAA by RRA serum (Chew et al., 2008).

ADRs: adverse drug reactions. TCAs: tricyclic antidepressants. SAA by RRA: serum anticholinergic activity by radioreceptor assay. Chew et al. (2008) described duloxetine as having questionable antimuscarinic activity.

Table 2. Antipsychotics with low or questionable antimuscarinic activity

ANTIPSYCHOTICS WITH LOW ANTIMUSCARINIC ACTIVITY	
- Loxapine.	In vitro studies (Davies et al., 2005; Fjalland et al., 1977; Miller & Hiley, 1976) and review articles (Carnahan et al., 2006; Rudolph et al., 2008) indicate loxapine may have low antimuscarinic activity but there are no clinical studies.
- Olanzapine.	In vitro studies (Bymaster & Falcone, 2000; Bymaster et al., 1999; Davies et al., 2005; Richelson, & Souder, 2000); animal studies (Bymaster et al., 1996); brain imaging studies (Lavalaye et al., 2001; Raedler, 2007; Raedler et al., 2000); SAA by RRA (Chengappa et al., 2000; Chew et al., 2006; Mulsant et al., 2004); and ADR case reports (Cohen et al., 2007) indicate olanzapine has low antimuscarinic activity. Reviews comparing antimuscarinic ADRs versus placebo indicate a small increase compared with placebo (Kantrowitz & Citrome, 2008). Some reviews of clinical trials by the company showed no increased antimuscarinic ADRs (Kennedy et al., 2000; 2001).
- Quetiapine:	In vitro studies (Davies et al., 2005; Goldstein & Brecher, 2000; Richelson & Souder, 2000; Saller & Salama, 1993); SAA by RRA (Chew et al., 2006) and review of antimuscarinic ADRs in clinical trials (de Leon, 2011) indicate that quetiapine has low antimuscarinic activity that may be relevant in some patients taking high doses, according to ADR cases (Raedler et al., 2007; Sokolski et al., 2004).
ANTIPSYCHOTICS WITH QUESTIONABLE ANTIMUSCARINIC ACTIVITY	
- Fluphenazine:	Positive data: According to review (Rudolph et al., 2008). Negative data: In vitro studies (Davies et al., 2005; Fjalland et al., 1977; Richelson & Divinetz-Romero, 1977; Snyder et al., 1974).
- Haloperidol:	Positive data: According to review (Rudolph et al., 2008). Negative data: In vitro studies (Davies et al., 2005; Fjalland et al., 1977; Hanley & Iversen, 1978; Richelson & Dvinetz-Romero, 1977; Snyder et al., 1974; Syvälahti et al., 1987) and SAA by RRA (Chew et al., 2006; de Leon et al., 2003).
- Perphenazine:	Positive data: According to review (Rudolph et al., 2008). Negative data: In vitro studies (Davies et al., 2005; Fjalland et al., 1977; Richelson & Divinetz-Romero, 1977; Snyder et al., 1974; Syvälahti et al., 1987).
- Risperidone:	Positive data: According to review (Rudolph et al., 2008). Negative data: In vitro studies (Davies et al., 2005; Richelson & Souder 2000; van Beijsterveldt et al., 1994) and SAA by RRA (Chew et al., 2006, 2008; Mulsant et al., 2004; Tracy et al., 1988).
- Ziprasidone:	Positive data: According to review (Rudolph et al., 2008). Negative data: In vitro studies (Davies et al., 2005; Richelson & Souder, 2000) and SAA by RRA (Chew et al., 2006, 2008).

ADRs: adverse drug reactions. SAA by RRA: serum anticholinergic activity by radioreceptor assay. Other antipsychotics occasionally mentioned as antimuscarinic are molindone, pimozide, thiothixene and trifluoperazine (Carnahan et al., 2006; Rudolph et al., 2008) but in vitro studies do not support that activity (Cusack et al., 1994; Fjalland et al., 1977; Davies et al., 2005; Miller & Hiley, 1974).

Table 3. Other psychiatric drugs with questionable antimuscarinic activity

-Amantadine: Positive data: According to review (Rudolph et al., 2008).

Negative data: In vitro study (Cusack et al., 1994; Davies et al., 2005).

-Benzodiazepines in general: Positive data: SSA by RRA (Tune et al., 1990). In a comprehensive Study, Chew et al., (2008) found that temazepam may have clinically relevant activity and diazepam questionable activity.

Negative data: They do not appear to bind to muscarinic receptors in vitro (Nordberg & Wahlström, 1992). Chew et al., (2008) found that most benzodiazepines have no SSA by RRA.

-Carbamazepine: Positive data: ADR case report (Hmouda et al., 2007) and review (Carnahan et al., 2006).

Negative data: In vitro study (Davies et al., 2005) and SSA by RRA (Chew et al., 2008).

-Lithium: Positive data: SSA by RRA (Chew et al., 2008).

Negative data: Lithium is thought to have complex effects in the cholinergic system but its actions are thought to promote cholinergic effects rather than anticholinergic effects in vitro (Tollefson et al., 1982-1983), animal models (Lerer & Stanley, 1985) and human models (Sokolski et al., 1999). Although most reviews do not consider lithium as antimuscarinic, they acknowledge that lithium can cause cognitive impairment (Wingo et al., 2009) due to its complex brain actions.

SAA by RRA: serum anticholinergic activity by radioreceptor assay.

A sophisticated study using SAA by RRA (Chew et al., 2008) included another psychiatric drug with questionable antimuscarinic activity: topiramate.

Table 4. Non-psychiatric drugs with questionable antimuscarinic activity

-Baclofen: Positive data: According to review (Rudolph et al., 2008).
 Negative data: In vitro study (Davies et al., 2005) and SAA by RRA (Chew et al., 2008).

-Cimetidine: Positive data: SAA by RRA (Tune et al., 1992).
 Negative data: May have agonist cholinergic effects (de Leon, 2011).

-Digoxin: Positive data: SAA by RRA (Tune et al., 1992).
 Negative data: Probably irrelevant SAA by RRA (Chew et al., 2008).

-Furosemide: Positive data: SAA by RRA (Tune et al., 1992).
 Negative data: Probably irrelevant SAA by RRA (Chew et al., 2008).

-Prednisolone: Positive data: SAA by RRA (Tune et al., 1992).

-Ranitidine: Positive data: SAA by RRA (Chew et al., 2008).
 Negative data: May have agonist cholinergic effects (de Leon, 2011).

-Theophylline: Positive data: SAA by RRA (Tune et al., 1992).
 Negative data: Animal models (Zarrindast et al., 1995).

SAA by RRA: serum anticholinergic activity by radioreceptor assay.

A sophisticated study using SAA by RRA (Chew et al., 2008) includes other non-psychiatric drugs with questionable antimuscarinic activity: amoxicillin, celecoxib, cephalexin, fentanyl, diphenoxylate, hydrocodone, lansaprazole, levofloxacin, metformin, phenytoin, and propoxyphene. Colchicine is another drug frequently described as having potential for antimuscarinic activity (Carnaham et al., 2008)

Table 5. Drugs with antimuscarinic activity in alphabetical order

	DEFINITIVE ACTIVITY	POSSIBLE ACTIVITY ^a
A	Amitriptyline	Amoxapine
B	Benztropine	Brompheniramine
C	Chlorpromazine Clemastine Clomipramine Clozapine Cyclobenzaprine Cyproheptadine	Carbinoxamine Cetirizine Chlorpheniramine Cimetidine
D	Darifenacin Dicyclomine Dimenhydrinate Diphenhydramine Disopyramide Doxepin	Desipramine Desloratidine
F	Fesoterodine Flavoxate	
G	Glycopyrrolate	
H	Hyoscyamine products	Hydroxyzine
I	Imipramine	Ipratropium
L		Levocetirizine Loratidine Loxapine
M		Maprotiline Meclizine Mirtazapine
N	Nortriptyline	
O	Orphenadrine Oxybutynin	Olanzapine
P	Prochlorperazine Procyclidine Promethazine Propantheline Protriptyline	Paroxetine
Q		Quetiapine
R		Ranitidine
S	Scopolamine Solifenacin	
T	Thioridazine Tiotropium Tolterodine Trihexyphenidyl Trimipramine Trospium	Temazepam

^aAccording to Chew et al. (2008), other drugs with low but definitive antimuscarinic activity are citalopram, escitalopram, fluoxetine and lithium and those with questionable activity are: amoxicillin, celecoxib, cephalexin, diazepam, digoxin, diphenoxylate, duloxetine, fentanyl, furosemide, hydrocodone, lansaprazole, levofloxacin, metformin, phenytoin, propoxyphene and topiramate. Other drugs described as having questionable activity are theophylline and prednisolone (Tune et al., 1992) and sertraline (Carnaham et al., 2006; Richelson, 2003).

Appendix 1: Drug utilization review: drugs with anticholinergic activity

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
DRUGS WITH ANTICHOLINERGIC ACTIVITY				
		YES	NO	NA
A) Drugs with definitive antimuscarinic activity		<input type="checkbox"/>	<input type="checkbox"/>	
	Antiparkinsonians: <input type="checkbox"/> benztropine, <input type="checkbox"/> procyclidine, or <input type="checkbox"/> trihexyphenidyl.			
	Antidepressants : <input type="checkbox"/> amitriptyline, <input type="checkbox"/> clomipramine, <input type="checkbox"/> doxepin, <input type="checkbox"/> imipramine, <input type="checkbox"/> nortriptyline, <input type="checkbox"/> protryptiline, or <input type="checkbox"/> trimipramine.			
	Antipsychotics: <input type="checkbox"/> chlorpromazine, <input type="checkbox"/> clozapine, or <input type="checkbox"/> thioridazine.			
	Antiemetics: <input type="checkbox"/> meclizine, <input type="checkbox"/> promethazine, or <input type="checkbox"/> prochlorperazine.			
	Drugs for peptic ulcer: <input type="checkbox"/> hyoscyamine, or <input type="checkbox"/> propantheline.			
	<input type="checkbox"/> Glycopyrrolate.			
	Muscle relaxants: <input type="checkbox"/> cyclobenzaprine, or <input type="checkbox"/> orphenadrine.			
	Cyproheptadine <input type="checkbox"/> .			
	Bronchodilators: <input type="checkbox"/> tiotropium.			
	Antiarrhythmics: <input type="checkbox"/> disopyramide.			
	Drugs for dizziness: <input type="checkbox"/> scopolamine.			
	Antispasmodic agents: <input type="checkbox"/> dicyclomine.			
	Treatment for overactive bladders: <input type="checkbox"/> darifenacin, <input type="checkbox"/> fesoterodine, <input type="checkbox"/> flavoxate, <input type="checkbox"/> oxybutynin, <input type="checkbox"/> oxybutynin transdermal system, <input type="checkbox"/> solifenacin, <input type="checkbox"/> tolterodine, or <input type="checkbox"/> trospium.			
	Some first-generation oral antihistamines: <input type="checkbox"/> clemastine, <input type="checkbox"/> dimenhydrinate, <input type="checkbox"/> or diphenhydramine.			
B) Polypharmacy of drugs with anticholinergic activity (≥ 2 meds with definitive antimuscarinic activity). Two were checked above.		<input type="checkbox"/>	<input type="checkbox"/>	
	Described in the chart by the psychiatrist as taking polypharmacy of drugs with anticholinergic activity. The patients will be more closely monitored for sedation and cognitive deficits, and the psychiatrist needs to comment on the risk and benefits of this type of polypharmacy. If the anticholinergic medications are not for psychiatric purposes, the family medicine physician or similar clinician can be responsible for this documentation.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Answer Yes (polypharmacy of drugs with anticholinergic activity was present and documentation was present), or No (polypharmacy of drugs with anticholinergic activity was present and documentation was absent) or NA (polypharmacy of drugs with anticholinergic activity was absent).</i>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C) Drugs with possible antimuscarinic activity		<input type="checkbox"/>	<input type="checkbox"/>	
	Antidepressants: <input type="checkbox"/> amoxapine, <input type="checkbox"/> desimipramine, <input type="checkbox"/> maprotiline, <input type="checkbox"/> mirtazapine, or <input type="checkbox"/> paroxetine.			
	Antipsychotics: <input type="checkbox"/> loxapine, <input type="checkbox"/> olanzapine, or <input type="checkbox"/> quetiapine.			
	<input type="checkbox"/> Temazepam.			
	Some first-generation oral antihistamines: <input type="checkbox"/> brompheniramine, <input type="checkbox"/> carbinoxamine, <input type="checkbox"/> chlorpheniramine, or <input type="checkbox"/> hydroxyzine.			
	Some second generation oral antihistamines: <input type="checkbox"/> cetirizine, <input type="checkbox"/> desloratidine, <input type="checkbox"/> levocetirizine, or <input type="checkbox"/> loratidine.			
	Some H ₂ antagonists: <input type="checkbox"/> cimetidine, or <input type="checkbox"/> ranitidine.			
D) Other situations with potential risk of polypharmacy with drugs with anticholinergic activity: Check if any of the following is present:		<input type="checkbox"/>	<input type="checkbox"/>	

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
DRUGS WITH ANTICHOLINERGIC ACTIVITY				
		YES	NO	NA
<input type="checkbox"/>	1) One drug from definitive list (see Section A) _____ <input type="checkbox"/> and one drug from possible list (see Section C) _____ <input type="checkbox"/> .			
<input type="checkbox"/>	2) Presence of drug/s with definitive antimuscarinic activity (see Section A) _____ with its/their actions potentially increased by pharmacokinetic DDIs: 2.1) <input type="checkbox"/> . Taking at least one CYP2D6 drug with definitive antimuscarinic activity: <input type="checkbox"/> benztropine, <input type="checkbox"/> chlorpheniramine, <input type="checkbox"/> chlorpromazine, <input type="checkbox"/> darifenacin, <input type="checkbox"/> diphenhydramine, <input type="checkbox"/> fesoterodine, <input type="checkbox"/> promethazine, <input type="checkbox"/> thioridazine, or <input type="checkbox"/> tolterodine. AND a CYP2D6 inhibitor: <input type="checkbox"/> bupropion, <input type="checkbox"/> duloxetine, <input type="checkbox"/> fluoxetine, or <input type="checkbox"/> paroxetine. 2.2) <input type="checkbox"/> . Taking at least one CYP1A2 drug with definitive antimuscarinic activity: <input type="checkbox"/> clozapine, or <input type="checkbox"/> cyclobenzaprine. AND a CYP1A2 inhibitor: <input type="checkbox"/> ciprofloxacin, <input type="checkbox"/> cimetidine, <input type="checkbox"/> fluvoxamine, or <input type="checkbox"/> high caffeine levels. 2.3) <input type="checkbox"/> . Taking at least one CYP3A drug: <input type="checkbox"/> disopyramide, <input type="checkbox"/> fesoterodine, <input type="checkbox"/> oxybutynin, or <input type="checkbox"/> solifenacin. AND a CYP3A inhibitor: <input type="checkbox"/> clarithromycin, <input type="checkbox"/> diltiazem, <input type="checkbox"/> erythromycin, <input type="checkbox"/> fluconazole, <input type="checkbox"/> fluoxetine, <input type="checkbox"/> fluvoxamine, <input type="checkbox"/> itraconazole, <input type="checkbox"/> ketoconazole, or <input type="checkbox"/> other _____. 2.4) <input type="checkbox"/> . Taking <input type="checkbox"/> a TCA _____ and <input type="checkbox"/> CYP2D6, <input type="checkbox"/> CYP1A2 or <input type="checkbox"/> CYP3A inhibitors _____.			
<input type="checkbox"/>	3) Presence of drug/s with definitive anticholinergic activity (see Section A) _____ with its/their actions potentially increased by pharmacodynamic DDIs. 3.1) <input type="checkbox"/> Increased risk of tachycardia: Taking at least one of: <input type="checkbox"/> amlodipine, <input type="checkbox"/> amphetamines, <input type="checkbox"/> atomoxetine, <input type="checkbox"/> felodipine, <input type="checkbox"/> isradipine, <input type="checkbox"/> methylphenidate, <input type="checkbox"/> modafinil, or <input type="checkbox"/> nifedipine. 3.2) <input type="checkbox"/> Increased risk of delayed gastric emptying: Taking <input type="checkbox"/> pramlintide. 3.3) <input type="checkbox"/> Increased risk of constipation: Taking <input type="checkbox"/> antacids containing aluminum or calcium, <input type="checkbox"/> any calcium channel blocker _____, <input type="checkbox"/> calcium supplements, <input type="checkbox"/> cholestyramine, <input type="checkbox"/> colestipol, <input type="checkbox"/> clonidine, <input type="checkbox"/> any diuretic _____, <input type="checkbox"/> iron supplements, <input type="checkbox"/> levodopa, <input type="checkbox"/> any NSAID _____, <input type="checkbox"/> any opioid _____ and <input type="checkbox"/> any vinca alkaloid _____. 3.4) <input type="checkbox"/> Increased risk of heat stroke due to taking at least one of: <input type="checkbox"/> acetazolamide, <input type="checkbox"/> antipsychotic not anticholinergic, <input type="checkbox"/> topiramate or <input type="checkbox"/> zonisamide; or exposure to <input type="checkbox"/> hot weather and/or <input type="checkbox"/> strenuous exercise; or <input type="checkbox"/> age \geq 65 years.			
<input type="checkbox"/>	4) Presence of drug/s with definitive anticholinergic activity (see Section A) _____ with its/their actions potentially increased by personal characteristics. 4.1) <input type="checkbox"/> Dry eyes and/or dry mouth: Sjogren syndrome <input type="checkbox"/> .			
	4.2) <input type="checkbox"/> Already having tachycardia <input type="checkbox"/> or patients in whom increased heart rate is not recommended.			
	4.3) <input type="checkbox"/> Already constipated <input type="checkbox"/> or having decreased GI motility <input type="checkbox"/> .			
	4.4) <input type="checkbox"/> Prone to urinary retention <input type="checkbox"/> or with benign prostate hyperplasia <input type="checkbox"/> .			
	4.5) <input type="checkbox"/> Elderly (age \geq 65 years) <input type="checkbox"/> or,			
	4.6) <input type="checkbox"/> Demented.			
E) Documentation for other situations with potential risk of polypharmacy with drugs with anticholinergic activity: At least one of the boxes to the left of D1, D2, D3 or D4 were checked:				
	The pharmacist documents on these situations of lower risks for	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
DRUGS WITH ANTICHOLINERGIC ACTIVITY				
		YES	NO	NA
	polypharmacy with anticholinergic activity in the pharmacy section in the psychiatric assessments focusing on DDI. Moreover, the pharmacist is responsible for reminding the psychiatrist or family medicine physician when any of these situations may have clinical relevance and/or are contributing to ADRs. If the psychiatrist or family medicine physician or similar clinician (if medications are not for psychiatric purposes) documents these situations, this will meet the requirement for documentation.			
	<i>Answer Yes (other situations with potential risk of polypharmacy of drugs with anticholinergic activity was present and documentation was present), or No (other situations with potential risk of polypharmacy of drugs with anticholinergic activity was present and documentation was absent) or NA (other situations with potential risk of polypharmacy of drugs with anticholinergic activity was absent).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F) Drug with antimuscarinic activity in the presence of acetylcholinesterase inhibitors:		<input type="checkbox"/>	<input type="checkbox"/>	
	<p>Taking an acetyl cholinesterase inhibitor: <input type="checkbox"/> donepezil, <input type="checkbox"/> galantamine, <input type="checkbox"/> rivastigmine, or <input type="checkbox"/> tacrine.</p> <p>1) At least one drug from definitive list _____(see Section A). This combination should not be used. If it is present there is major justification using very careful documentation <input type="checkbox"/> or there is a documented plan for discontinuation of the drug with definitive antimuscarinic activity <input type="checkbox"/> or the acetylcholinesterase inhibitor<input type="checkbox"/>.</p> <p>2) One drug from possible list _____ (see Section C). This combination should be avoided. If it is present there is justification by very careful documentation<input type="checkbox"/>.</p>			
	<i>Answer Yes (drug with antimuscarinic activity in the presence of acetylcholinesterase inhibitors and documentation was present), or No (drug with antimuscarinic activity in the presence of acetylcholinesterase inhibitors and documentation was absent) or NA (drug with antimuscarinic activity in the presence of acetylcholinesterase inhibitors was absent).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix 2: Drug utilization review: oral benztropine

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
ORAL BENZTROPINE				
		YES	NO	NA
1) Indication: <i>Check one of the following indications for use</i>				
<input type="checkbox"/>	Adjunctive treatment in Parkinson disease.			
<input type="checkbox"/>	Reversible antipsychotic-induced extrapyramidal symptoms (EPS) (acute dystonic reactions, parkinsonism and akathisia). Acute dystonic reactions usually respond well to anticholinergic medications. Antipsychotic-induced parkinsonism usually responds to anticholinergic medication. When akathisia is associated with other reversible EPS, anticholinergic medication such as benztropine may be the first choice, but in other akathisia situations, anticholinergic medications may be a second or third choice. Rabbit syndrome is a parkinsonian orofacial tremor that occurs after prolonged antipsychotic use; it usually responds to anticholinergic medication.			
<input type="checkbox"/>	EPS prophylaxis. Use as a prophylaxis for reversible antipsychotic-induced EPS in highly vulnerable patients, particularly for those with a history of acute dystonic reactions.			
<input type="checkbox"/>	Primary or tardive dystonia. The literature reports that primary dystonia or tardive dystonia may respond to high doses of anticholinergics. For this indication, the chart should note that an expert with experience in this area has been consulted and approves the use of high doses of anticholinergics (Y___ N___).			
<input type="checkbox"/>	Hypersalivation. Anticholinergics including benztropine have been used to treat hypersalivation, including cases associated with clozapine treatment. Other treatments with less risk of adverse drug reactions (ADRs) have been considered (Y___ N___).			
<input type="checkbox"/>	Other uses less frequently described in the literature. These require an explanatory note in the chart justifying the benztropine use. The treatment of antidepressant-induced sweating is an example.			
<i>To meet indication criteria at least one indication is present and documented.</i>		<input type="checkbox"/>	<input type="checkbox"/>	
2) Dose: Dose_____ and administration pattern_____				
	For treatment of antipsychotic-induced EPS, the recommended oral dose for adults with is 1-4 mg administered 1-2 times a day. There is no clearly agreed maximum recommended daily dose in the literature; doses up to 8 mg/day have been described. Thus, any dose > 8 mg/day was justified in the chart with a very thorough discussion validating the usage of higher doses and verifying that no ADRs are present (Y_ N_).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	For prophylaxis of antipsychotic-induced EPS, doses up to 4 mg/day have been recommended. Thus, any dose > 4 mg/day was justified in the chart with a very thorough discussion validating the usage of higher doses and verifying that no ADRs are present (Y_ N_).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Taking CYP2D6 inhibitors (e.g., fluoxetine_, paroxetine_, bupropion_, duloxetine_, or other_____). The chart documents the interaction.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Benztropine may have additive sedative effects when combined with other sedating drugs, including anticonvulsants_, antihistamines_, benzodiazepines_, opioids_, some antidepressants_ and some antipsychotics_.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Benztropine may have additive antimuscarinic effects when combined with other antimuscarinic drugs: antidepressants (amitriptyline_, clomipramine_, doxepin_, imipramine_, nortriptyline_, protriptyline_, or trimipramine_); antipsychotics (chlorpromazine_, clozapine_, or thioridazine_); some antiemetics (meclizine_, promethazine_ or prochlorperazine_); some drugs for peptic ulcer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
ORAL BENZTROPINE				
		YES	NO	NA
	(hyoscyamine__ or propantheline__); glycopyrrolate__; some muscle relaxants (cyclobenzaprine__, or orphenadrine__); cyproheptadine__; some bronchodilators (tiotropium__); some antiarrhythmics (disopyramide__); some drugs for dizziness (scopolamine__); drugs for overactive bladders (darifenacin__, fesoterodine__, flavoxate__, oxybutynin__, oxybutynin transdermal system__, solifenacin__, tolterodine__, or trospium__); and some first-generation oral antihistamines (clemastine__; dimenhydrinate__; or diphenhydramine__). The chart documents (Y_N_) that the patient meets criteria for Polypharmacy of Drugs with Drugs with Anticholinergic Activity.			
	Lower risks are present for other drugs with possible antimuscarinic activity including some antidepressants (amoxapine__, desipramine__, maprotiline__, mirtazapine__, or paroxetine__); some antipsychotics (loxapine__, olanzapine__, or quetiapine__); ipratropium and some oral antihistamines (brompheniramine__, carbinoxamine__, cetirizine__, chlorpheniramine__, desloratidine__, hydroxyzine__, levocetirizine__, or loratidine__); some H ₂ antagonists (cimetidine__ or ranitidine__) and temazepam__. The chart documents (Y_N_) that the patient meets criteria for Potential Risk of Polypharmacy of Drugs with Drugs with Anticholinergic Activity.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Other drugs that can cause tachycardia include stimulant and related drugs (amphetamines__, methylphenidate__, atomoxetine__, or modafinil__), and some calcium channel blockers (amlodipine__, felodipine__, isradipine__, or nifedipine__). The chart documents (Y__ N__) that the potential of additive effects in heart frequency has been considered.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Pramlintide can decrease gastric motility. The chart documents (Y__ N__) that the potential of additive effects in gastric motility has been considered.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Medications that can contribute to constipation include antacids containing aluminum __ or calcium__, calcium channel blockers__, calcium supplements__, cholestyramine__ or colestipol__, clonidine__, diuretics__, iron supplements__, levodopa__, NSAIDs__, opioids__ and vinca alkaloids __. The chart documents (Y__ N__) the potential of additive effects with greater risk for constipation and ileus.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Benztropine can definitively cause anhydrosis by parasympathicomimetically inhibiting sweat secretion, thus contributing to hyperthermia and heat stroke risk. There is more risk if 1) the patient is taking other drugs that may potentiate antimuscarinic effects, including antipsychotics __ and carbon anhydrase inhibitors (acetazolamide__, topiramate__ or zonisamide__); 2) exposure exposed to heat__ and/or strenuous exercise__ and 3) with geriatric age (≥ 65 years old)__. The chart documents (Y__ N__) the potential risks.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Other anticholinergics used for their antiparkinsonian activity (biperiden __, diphenhydramine__, procyclidine__, and trihexyphenidyl__) or acetylcholinesterase inhibitors (donepezil__, galantamine__, rivastigmine__ or tacrine__). The chart documents (Y__ N__) the discontinuation plan.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Geriatric (≥ 65 years old). Any dose > 2 mg/day was justified in the chart with a very thorough discussion validating the usage of higher doses and verifying that no ADRs are present (Y__ N__).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Hepatic __or renal impairment __. The chart documents (Y__ N__) that lower doses are used.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>To meet dose criteria all are Yes or NA.</i>		<input type="checkbox"/>	<input type="checkbox"/>	

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
ORAL BENZTROPINE				
		YES	NO	NA
3) Relative contraindications: <i>Check left boxes of any present</i>				
<input type="checkbox"/>	Patient personal characteristics, present before starting benztropine, may increase ADR risk: Sjogren syndrome__ ; preexisting tachycardia__ or patients in whom increased heart rate is not recommended__ ; preexisting constipation __and/or decreased GI motility__ ; prone to urinary retention __and/or with benign prostate hyperplasia__ ; geriatric patient (≥ 65 years old) __ ; demented patient__ ; or tardive dyskinesia__ .			
<input type="checkbox"/>	Intake of drugs that may have pharmacodynamic DDI that can potentiate benztropine. Drugs that a) increase heart rate including stimulant and related drugs (amphetamines__ , methylphenidate__ , atomoxetine__ , or modafinil__) , or some calcium channel blockers (amlodipine__ , felodipine__ , isradipine__ , or nifedipine__) ; b) decrease gastric motility: pramlintide__ ; c) increase constipation risk including antacids containing aluminum__ or calcium__ , calcium channel blockers__ , calcium supplements__ , cholestyramine__ and colestipol__ , clonidine__ , diuretics__ , iron supplements__ , levodopa__ , NSAIDs__ , opioids__ or vinca alkaloids__ ; or d) contribute to heat stroke risk: taking antipsychotics__ or carbon anhydrase inhibitors (acetazolamide__ , topiramate__ or zonisamide__) or with exposure to hot weather__ or strenuous exercise__ .			
<input type="checkbox"/>	Taking other anticholinergics used for their antiparkinsonian activity (biperiden __ , diphenhydramine__ , procyclidine__ , or trihexyphenidyl__) or acetylcholinesterase inhibitors (donepezil__ , galantamine__ , rivastigmine__ or tacrine__) .			
<i>Answer Yes if none is checked, or if any of the above are checked but rationale is documented in the chart to meet relative contraindication criteria. Answer No if rationale is NOT documented in the chart.</i>		<input type="checkbox"/>	<input type="checkbox"/>	
4) Discontinuation:				
	For treating reversible EPS. A) Benztropine was tapered off slowly over weeks or months (Y__ N__) to minimize the potential of cholinergic rebound signs and the relapse of antipsychotic-induced EPS, unless it was not possible for medical reasons __ . B) Periodic attempts were made to wean anticholinergics in a patient taking benztropine chronically for any reversible EPS to avoid increasing the risk of tardive dyskinesia. These attempts are documented and reviewed at least annually (Y__ N__) .	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	For preventing reversible EPS. When benztropine is used to prevent acute dystonic reactions, the chart documents the attempt to wean the dose slowly over 10 days while watching for the development of parkinsonism or akathisia.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8) Adverse drug reactions (ADRs) due to benztropine: <i>Check left boxes to indicate which ADRs are present</i>				
8.1) Common ADRs:				
<input type="checkbox"/>	Sedation.			
<input type="checkbox"/>	CNS antimuscarinic blockade: Memory deficits, sleep disturbances, more global cognitive deficits, or even delirium with or without hallucinations.	<input type="checkbox"/>	Peripheral antimuscarinic blockade: decreased sweating, mydriasis, blurred vision, decreased lacrimation, decreased and thickened bronchial secretions, increased heart rate, dry mouth, nasal dryness, decreased gastric	

DRUG UTILIZATION REVIEW CRITERIA				CRITERIA MET		
ORAL BENZTROPINE						
				YES	NO	NA
			acidity and delayed gastric emptying, constipation, or urinary retention			
8.2) Relatively uncommon ADRs:						
<input type="checkbox"/>	Skin rash.	<input type="checkbox"/>	Abuse.			
<input type="checkbox"/>	Other _____	<input type="checkbox"/>	Other _____			
8.3) Potentially lethal ADRs:						
<input type="checkbox"/>	Hyperthermia and/or heat stroke.					
Answer Yes (intervention or benefit/risk discussion after ADRs developed) or No (neither intervention nor benefit/risk discussion after ADRs developed) or NA (no abnormality developed).				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix 3: Drug utilization review: parenteral benztropine

DRUG UTILIZATION REVIEW CRITERIA		CRITERIA MET		
PARENTERAL BENZTROPINE				
		YES	NO	NA
1) Indication : <i>Check one of the following indications for use</i>				
<input type="checkbox"/>	Antipsychotic-induced acute dystonic reactions or any other form of severe antipsychotic-induced extrapyramidal symptoms (EPS).			
<input type="checkbox"/>	EPS prophylaxis. Co-administer with an IM antipsychotic including standard _____ or long-acting antipsychotic formulations _____ for prophylaxis of reversible antipsychotic-induced EPS in highly vulnerable patients, particularly for those with a history of acute dystonic reactions.			
<i>To meet indication criteria at least one indication is present.</i>		<input type="checkbox"/>	<input type="checkbox"/>	
2) Dose: Describe in each episode the doses (mg, route and administration time): _____.				
	When treating EPS: Dose, repetitions and route are justified by severity of situation (most times parenteral benztropine is administered IM). Recommended doses for acute dystonic reactions in adults are up to 2 mg. The dose can be repeated in 20 minutes if there is no response. In special circumstances such as severe acute dystonic reactions including laryngeal dystonia, the IV route may be preferable; 4 mg should be used and doses can be repeated in 10 minutes.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	When treating EPS: If the parenteral benztropine was effective, oral benztropine was used (describe pattern) _____ or considered (chart includes a note: Yes___ No ___) to avoid relapses after the rapid elimination of the drug administered parenterally.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Prophylactic doses. Doses appear reasonable (1-2 mg) (Y__N_) or prior history (Y__N__) was used to guide dosing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>To meet dose criteria all are Yes or NA.</i>		<input type="checkbox"/>	<input type="checkbox"/>	
3) Adverse drug reactions (ADR) due to IM Benztropine: <i>Check left boxes to indicate which ADRs are present.</i>				
3.1) Common ADRs:				
<input type="checkbox"/>	Sedation.			
<input type="checkbox"/>	CNS antimuscarinic blockade: Memory deficits, sleep disturbances, more global cognitive deficits, or even delirium with or without hallucinations.	<input type="checkbox"/>	Peripheral antimuscarinic blockade: decreased sweating, mydriasis; blurred vision, decreased lacrimation, decreased and thickened bronchial secretions; increased heart rate, dry mouth, nasal dryness, decreased gastric acidity and delayed gastric emptying, constipation, or urinary retention	
3.2) Relatively uncommon ADRs:				
<input type="checkbox"/>	Skin rash.	<input type="checkbox"/>	Abuse.	
<input type="checkbox"/>	Other _____.	<input type="checkbox"/>	Other _____.	
3.3) Potentially lethal ADRs:				
<input type="checkbox"/>	Hyperthermia and/or heat stroke.			
<i>If any ADR is present check Yes (this prompted some intervention and consideration of risk/benefit for future injections) or No. If no ADRs are present check NA.</i>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>