PROPHYLACTIC ANTICHOLINERGIC MEDICATION TO PREVENT DRUG-INDUCED ACUTE EXTRAPYRAMIDAL SIDE EFFECTS: A SYSTEMATIC REVIEW

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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This thesis is dedicated to Dr. John A. Sarko who dedicated his life to the education and care of others.

Abstract:

Introduction: Neuroleptic medications are commonly administered in the emergency department but are known to induce extrapyramidal symptoms (EPS) in some patients; typically dystonia and akathisia. This systematic review will examine if adjunctive medications are efficacious when given in conjunction with neuroleptic medications to prevent these extrapyramidal symptoms.

Methods: The Central, DARE, LILACS, PubMed, CINAHL, and OVID databases were searched for relevant articles between January 2014 and February 2016. Inclusion criteria required the article to be a randomized controlled trial; administer an anticholinergic medication given concurrently or just prior to treatment with medications with known extrapyramidal side effects; and be published in English.

Results: The initial search strategy yielded 1222 prospective articles of which 1208 were excluded by title and/or abstract. Fourteen articles were retrieved in full text and independently reviewed by each author. Seven 7 RCTs representing 645 patients were determined to be appropriate for analysis. Meta-analysis of 5 studies found a significant effect (OR 0.4 with 95% CI 0.23-0.71) for utilizing anticholinergic adjunct medications in the prevention of EPS for 60 minutes after administration. No reduction was found (OR 1.14 with 95% CI 0.01-164) in EPS after 60 minutes in meta-analysis of 2 studies with opposing results. Adjunctive anticholinergic medication was effective in reducing symptoms of dystonia (OR 0.13 with 95% CI 0.04-0.43) but not in reducing symptoms of akathisia (OR 0.74 with 95% CI 0.27-1.98).

Conclusion: This systematic review found that anticholinergic adjuvant anticholinergic treatment reduced EPS induced by antipsychotic medications during 60 minutes after administration, with the greatest reduction in dystonic symptoms.

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Figures and Tables

Introduction

Extrapyramidal symptoms (EPS) are a set of hyperkinetic movement disorders usually stemming from use of neuroleptic medications, such as haloperidol, or related medications, such as metoclopramide, an anti-emetic. This review will focus on two common acute EPS; dystonia and akathisia.

Dystonia is a grouping of sustained abnormal or involuntary muscle movements.[1] These movements can stem from various pathological states like Wilson's Disease or be pharmacologically induced as in the case of dystonia. Dystonia can be further divided into primary (having no identifiable cause) or secondary dystonias (having a known cause). Drug-induced dystonias will be the focus of this study. Akathisia is a sensation of restlessness and the perceived need for movement. It is often associated with use of neuroleptic medications.[2]

The pathophysiology of dystonia and akathisia is incompletely understood but the working hypothesis is that the symptoms occur due to antipsychotic-induced dopamine receptor (D2) occupancy above a threshold of 80%.[3] Cholinergic and adrenergic pathways may play a major role in regulation of symptoms.[3]

Electrophysiologically, dystonia is distinguished by a sustained, simultaneous contraction of agonist and antagonist muscles. Electrophysiological and imaging findings display loss of reflex inhibition in both spinal and brainstem reflexes as well as a loss of inhibitory patterns in the motor cortex. There is also evidence of sensory processing abnormalities. Slight impairment in temporal and spatial discrimination tasks, as well as somatosensory-evoked potentials is also observed.[4]

Neuroleptics are utilized in an emergency setting primarily for pharmacologic control of the acutely psychotic patient who is dangerous to themselves or others. In this scenario, haloperidol would likely be used. Episodes of delirium or general need for sedation may also be treated with neuroleptics. Metoclopramide can be used to control severe nausea and vomiting, and is also used in the treatment of acute migraine headache.

As noted, a proposed mechanism of action for the extrapyramidal effects of haloperidol and metoclopramide is the binding and antagonization of D_2 receptors. When >80% of the D_2 receptor are occupied by an antagonist, dopaminergic stimulation is decreased. It should be noted that several drugs that do not bind D_2 receptors (such as a selective serotonin reuptake inhibitor) are known to cause EPS. It is suggested that their mechanism of action involves direct stimulation of 5-HT_{2A} receptors.[6]

Incidence of acute drug-induced EPS is difficult to ascertain because of underreporting, lack of definitive diagnostic criteria, and the under-appreciation of mild to atypical cases. That said, the conservative estimate of acute akathisia induced by antipsychotics, antiemetics, and antidepressants is 30-40%.[7] This estimate includes all spectrums of akathisia in various settings. These reactions are more common in children, young adults and adolscents.[8]

The treatment of acute dystonia and other EPS symptoms with anticholinergic medications, such as diphenhydramine or benztropine. Anticholinergic medications are commonly utilized to prevent or treat emergence of EPS. This phenomenon is predicated on the reciprocal relationship of dopamine and acetylcholine in the Nigrostriatal pathway. Normally, dopamine suppresses acetylcholine activity, thus removal of dopamine inhibition will lead to increased acetylcholine activity. If D2 receptors on the cholinergic dendrite are blocked, acetylcholine will become overly active, resulting in production of EPS. Thus, the proposed pharmacological mechanism of EPS seems to be a relative dopamine deficiency and relative acetylcholine excess. Typical anti-psychotics with weak, inherent anticholinergic properties pose a risk of causing EPS. Conversely, those typical antipsychotics with greater anticholinergic properties will exhibit

fewer EPS. If anticholinergic medications (Benztropine, Diphenhydramine) are administered, then the relative acetylcholine excess and subsequent movement disorder is circumvented[17].

While treatment of acute drug-induced EPS is effective, prevention may be more desirable. One prospective study demonstrated 8% of patients receiving intravenous prochlorperazine developed severe akathisia compelling them to move about the emergency department disruptively until treatment could be given.[9]

Research Question: Are prophylactically administered adjunctive anticholinergic medications effective in preventing extrapyramidal symptoms resulting from treatment with medications in an acute setting?

Methods & Search Strategy

The purpose of this review was to determine if prophylactic treatment with anticholinergic medications was efficacious in prevention of drug-induced EPS. The inclusion criteria for the studies were:

1) Randomized controlled trials
2) An anticholinergic (benztropine, diphenhydramine) was given adjunctively or prior to treatment with medications with known extrapyramidal side effects.
3) The patient was treated with a medication with known extrapyramidal side effects (metoclopramide, haloperidol, prochlorperazine etc.)

We electronically searched the following internet websites: Central, DARE, LILCS, PubMed, CINAHL, and OVID between January 2014 and February 2016

We utilized the following search strategy:

1. Randomized Controlled Trials
   Clinical Trials
   Clinical Trial Registry

   Keywords: randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups

Combined as OR

2. Psychomotor Disorders
   Dystonic Disorders
   Psychomotor Agitation
   Movement Disorders
   Keywords: Dystonic Disorders or Psychomotor Disorders or Movement Disorders or Psychomotor Agitation or akathisia or dystonia or Psychomotor Agitation or Extrapyramidal Tracts or Movement Disorders

Combined as OR

3. Search Term Explode

Adrenergic Beta-Antagonists
Histamine H1 Antagonists
Histamine H2 Antagonists
Cholinergic Antagonists
Lorazepam
Keywords: Diphenhydramine or Dimenhydrinate or Benztropine or Trihexyphenidyl or Lorazepam or Diazepam or Midazolam or Benadryl or Atarax or Vistaril or Cogentin or Artane or Ativan or Valium or Versed or Antihistamine or Benzodiazepine or Anticholinergic or Adrenergic beta-Antagonists

Combined as OR

4. Search Term Explode

Prochlorperazine
Metoclopramide
Haloperidol
Droperidol
Antipsychotic Agents
Antipsychotic Agents, Phenothiazine
Antipsychotic Agents, Butyrophenone
Promethazine
Keywords: Butyrophenone or Phenothiazine or Prokinetic or Antihistamine or Neuroleptic or Neuroleptics or Prochlorperazine or Droperidol or Haloperidol or Metoclopramide or Haldol or Compazine or Reglan or Thorazine or Phenergan or Inapsine

Combined as OR

Search Term Explode (+) Major Concept

Randomized Controlled Trials
Histamine H1 Antagonists
Histamine H2 Antagonists
Adrenergic Beta-Antagonists
Clinical Trials
Psychomotor Disorders
Clinical Trial Registry
Dystonic Disorders
Adrenergic Antagonists
Cholinergic Antagonists

Keywords: (Randomized Controlled Trials or Clinical Trials or Clinical Trial Registry or randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups) AND (Psychomotor Disorders or Dystonic Disorders or Psychomotor Agitation or Movement Disorders or Dystonic Disorders or Psychomotor Disorders or Movement Disorders or Psychomotor Agitation or akathisia or dystonia or Psychomotor Agitation or Extrapyramidal Tracts or Movement Disorders) AND (Adrenergic Beta-Antagonists or Histamine H1 Antagonists or Histamine H2 Antagonists or Cholinergic Antagonists or Lorazepam or Diphenhydramine or Dimenhydrinate or Benztropine or Trihexyphenidyl or Lorazepam or Diazepam or Midazolam or Benadryl or Atarax or Vistaril or Cogentin or Artane or Ativan or Valium or Versed or Antihistamine or Benzodiazepine or Anticholinergic or Adrenergic beta-Antagonists) AND (Prochlorperazine or Metoclopramide or Haloperidol Droperidol or Antipsychotic Agents or Antipsychotic Agents or Phenothiazine or Antipsychotic Agents or Butyrophenone or Promethazine or Butyrophenone or Phenothiazine or Prokinetic or Antihistamine or Neuroleptic or Neuroleptics or Prochlorperazine or Droperidol or Haloperidol or Metoclopramide or Haldol or Compazine or Reglan or Thorazine or Phenergan or Inapsine)

The initial search yielded 1222 potential articles obtained from the different databases as follows:

Central:
Total Articles: 65
Title Exclusion: 55
Abstract Exclusion: 8
Possible Inclusion: 2

DARE:
Total Articles: 89
Title Exclusion: 75
Abstract Exclusion: 14
Possible Inclusion: 0

LILACS:
Total Articles: 10
Title Exclusion: 9
Abstract Exclusion: 1
Possible Inclusion: 0

PubMed:
Total Articles: 548
Title Exclusion: 313
Abstract Exclusion: 232
Possible Inclusion: 3

CINAHL:
Total Articles: 0
Title Exclusion:
Abstract Exclusion:
Possible Inclusion:

OVID:
Total Articles: 510
Title Exclusion: 297
Abstract Exclusion: 204
Possible Inclusion: 9

1208 articles were excluded by title and/or abstract review, leading 14 articles that were independently reviewed in full by each author (Figure 1).

All Databases:
Total Articles: 1222
Title Exclusion: 749
Abstract Exclusion: 459
Further Review: 14

After full review, 7 articles were excluded for not being randomized and/or not addressing the authors primary question, leaving 7 articles with a total of 645 patients felt to have met criteria for analysis.

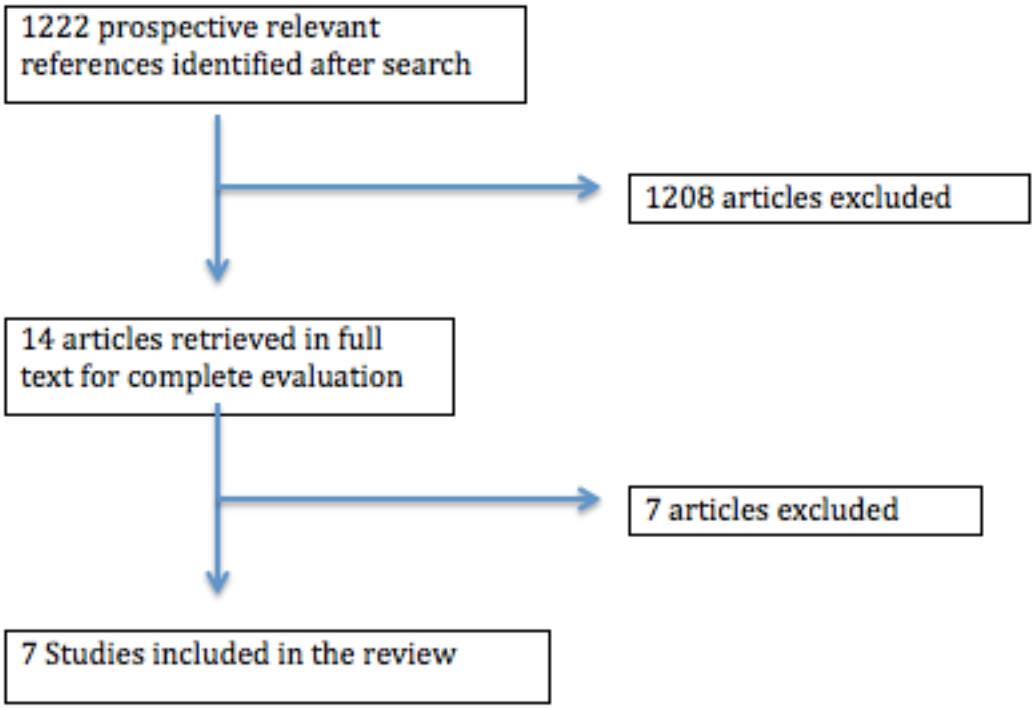

Figure 1. Search Strategy

Identification of Relevant Articles

Data from each article was extracted independently by each author with regular review to ensure consistent abstraction.

Abstraction of Data

Relevant data was abstracted from each study and is displayed in table 1.[10-16].

Author/year	RCT	Neuroleptic/EPS Drug Used	Anticholinergic Adjunct Used	Duration of study	Primary outcome	Secondary outcomes	Study population	Primary outcome	Secondary outcome
Winslow/1986	yes	Trifluoperazine, Thiothixene, Haloperidol, Fluphenazine (PO)	Benztropine 2mg PO daily	7 days	Occurance of acute dystonic reaction duing 7 days	Intensity of 4 anticholinergic symptoms: dry mouth, blurred vision, constipation, urinary hesitation	Control = 17 Intervention = 22	Control = 8/17 (47%) Intervention = 0/22 (0%)	no difference between control and intervention group
Vinson/2001	yes	Prochlorperazine 10mg IV	50mg Diphenhydramine IV given over 2 minutes	1 Hour	Incidence of akathisia 1 hour later	Rating of drowsiness	Control = 50 Intervention = 50	Control = 18/50 (36%) Intervention = 7/50 (14%)	Statistically Significant increase in drowsiness in intervention group
Goff/1991	yes	Haloperidol minimum dose of 5mg 2x IM, PO in days following	Benztropine 2mg PO	14 days	Occurance of acute dystonia	Anticholinergic Symptoms and Haloperidol Plasma Concentration	33 Enrolled, 4 withdrew. Control = 15 Intervention = 14 *Difference was not statistically significant.	Control = 5/15 (33%) Intervention = 2/14 (14%)	Diminished sweat, dry mouth and decrease in mean heart rate was observed in intervention group. Mean Haloperidol plasma levels were even among both groups.
Kostic/2009	yes	10mg Prochlorperazine and 6mg Sumatriptan	12.5 mg Diphenhydramine	80 Minutes	Mean change in pain	Side effects experienced (anticholinergic and nausea)	68 Enrolled, 66 completed.	Sumatriptan = 34/66 Prochlorperazine = 32/66 Prochlorperazine + Diphenhydramine was found to more significantly reduce migraine pain.	The side effects experienced were similar across both groups.
Friedman/2008	yes	10-20mg IV metoclopramide	25mg Diphenhydramine	60 Minutes	Development of akathisia	Dosage of Metoclopramide and development of akathisia	1) 10 mg Metoclopramide + Diphenhydramine 2) 10mg Metoclopramide + Placebo 3) 20mg Metoclopramide + Diphenhydramine 4) 20mg Metoclopramide + Placebo	1) 8/71 (11.3%) 2) 5/72 (6.9%) 3) 7/72 (9.7%) 4) 14/71 (19.7%)	10 mg Metoclopramide = 13/143 (9%) 20 mg Metoclopramide = 21/143 (15%)
Erder/2010	yes	Metoclopramine 10mg	Midazolam 1.5mg Diphenhydramine 20mg	60 minutes	Incidence of akathisia	Sedation	Metoclopramide + Midazolam = 75/225 (33%) Metoclopramide + Diphenhydramine = 75/225 (33%) Metoclopramide + Placebo = 75/225 (33%)	Midazolam = 5/75 (5.3%) Diphenhydramine = 10/75 (13.3%) Placebo = 16/75 (21.3%)	Midazolam = 60/75 (80%) Diphenhydramine = 38/75 (50.7%) Placebo = 20/75 (26.7%)
Stern/1979	yes	chlorpromazine or similar antipsychotic 200mg/day	Benztropine 2mg	2 Weeks - 6 Months with mean contact time of 12.7 weeks	Occurrence of Dystonia		82 patients initially, 39 lost to follow-up, 3 with incomplete data.	12/40 (30%) without prophylaxis. 1/40 (2.5%) with benzotropine prophylaxis.	

Table 1. Data Extraction Table after inclusion criteria

Meta-Analysis

The seven studies included in the review were subsequently grouped and analyzed based on various components of the studies.

Figure 2 examined prevention of EPS and were grouped by the length of observation for said symptoms. Acute symptoms were defined as emergence within 60 minutes of administration of the neuroleptic agent, while longer follow-up was defined as emergence after the 60 minute period. Results outlined in figure 2 demonstrate a 60% risk reduction of EPS when there is concomitant administration of an anticholinergic medication with a neuroleptic in an acute setting. No significant benefit was observed when follow up was greater than 60 minutes.

Figure 3 examined prevention of EPS, stratified by the type of symptom observed; namely dystonia or akathisia. When stratified as such and grouped the studies exhibited an 87% decrease in emergence of dystonia and a 26% decrease in the emergence of akathisia respectively.

Figure 4 examined the use of diphenhydramine as the adjunct to a neuroleptic in the prevention of EPS, but does not take into temporal emergence or the type of EPS exhibited. Results demonstrate a 57% decrease in emergence of symptoms when diphenhydramine is utilized versus other medications or a non-treatment group.

Figure 5 is a funnel plot utilized to assess the studies included for bias. When plotted, the data is presented as symmetric and inverted, suggesting bias within the studies was minimized.

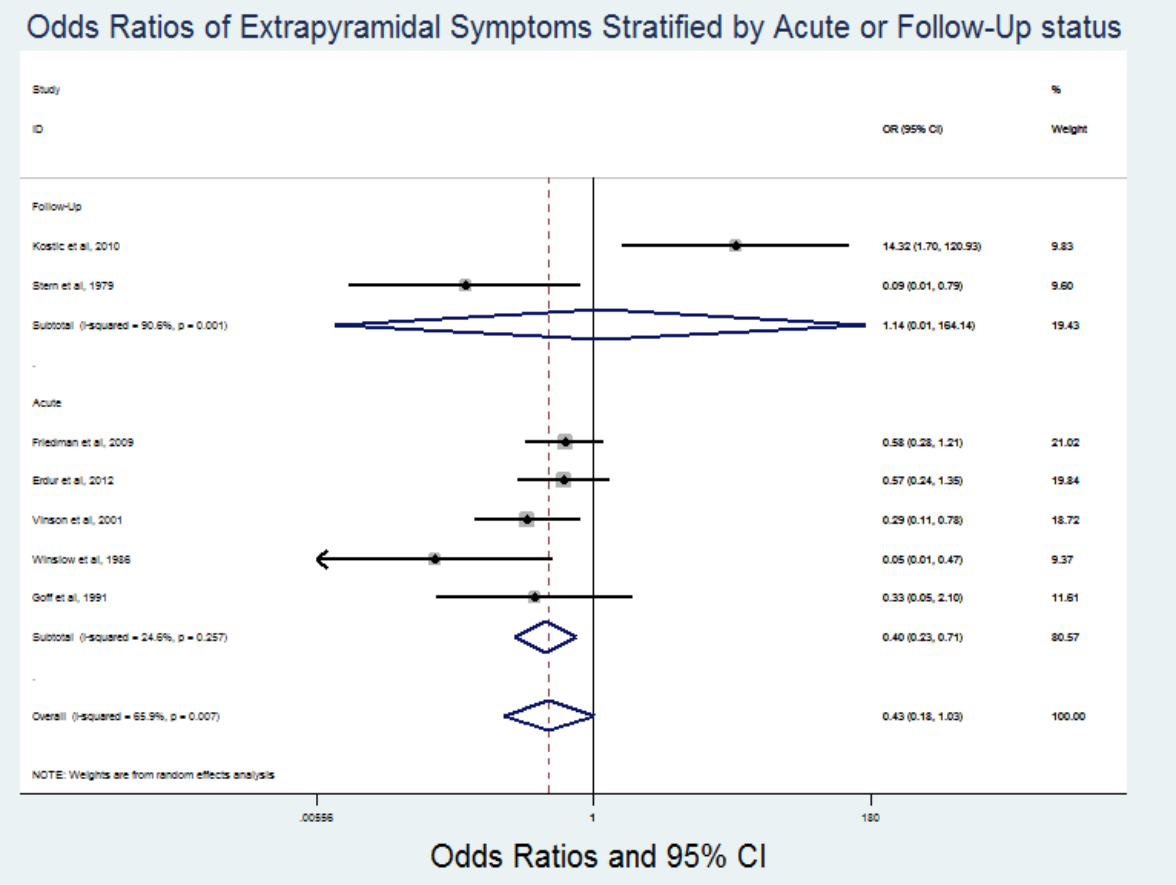

Figure 2. This figure demonstrates a significant effect of utilizing adjunct medications in the prevention of EPS in an acute setting. In studies where follow up was greater than 60 minutes, there is no significant benefit. The risk reduction in an acute setting is 60%.

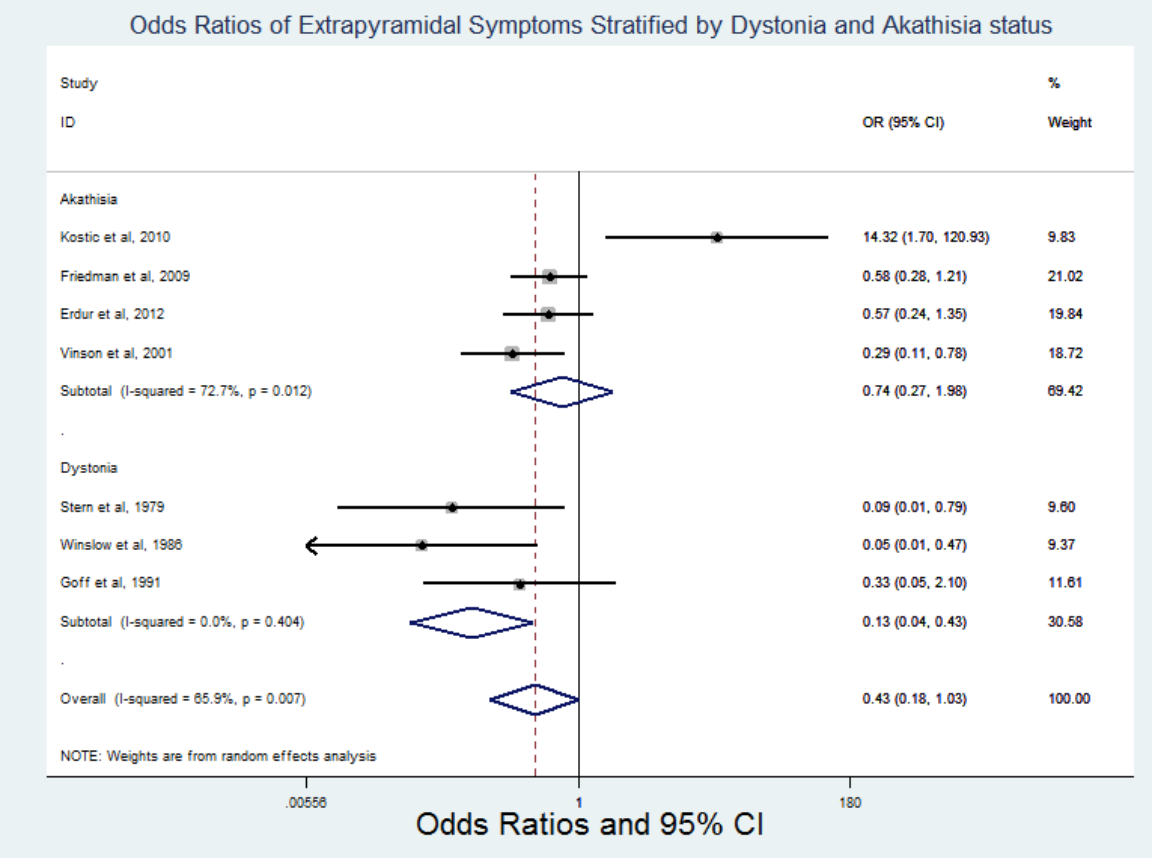

Figure 3. This figure demonstrates that utilization of adjunct medications to prevent dystonia is more significant that utilization to prevent akathisia. Utilization of adjunctive medication results in a decrease in risk of 87% and 26% for dystonia and akathisia respectively.

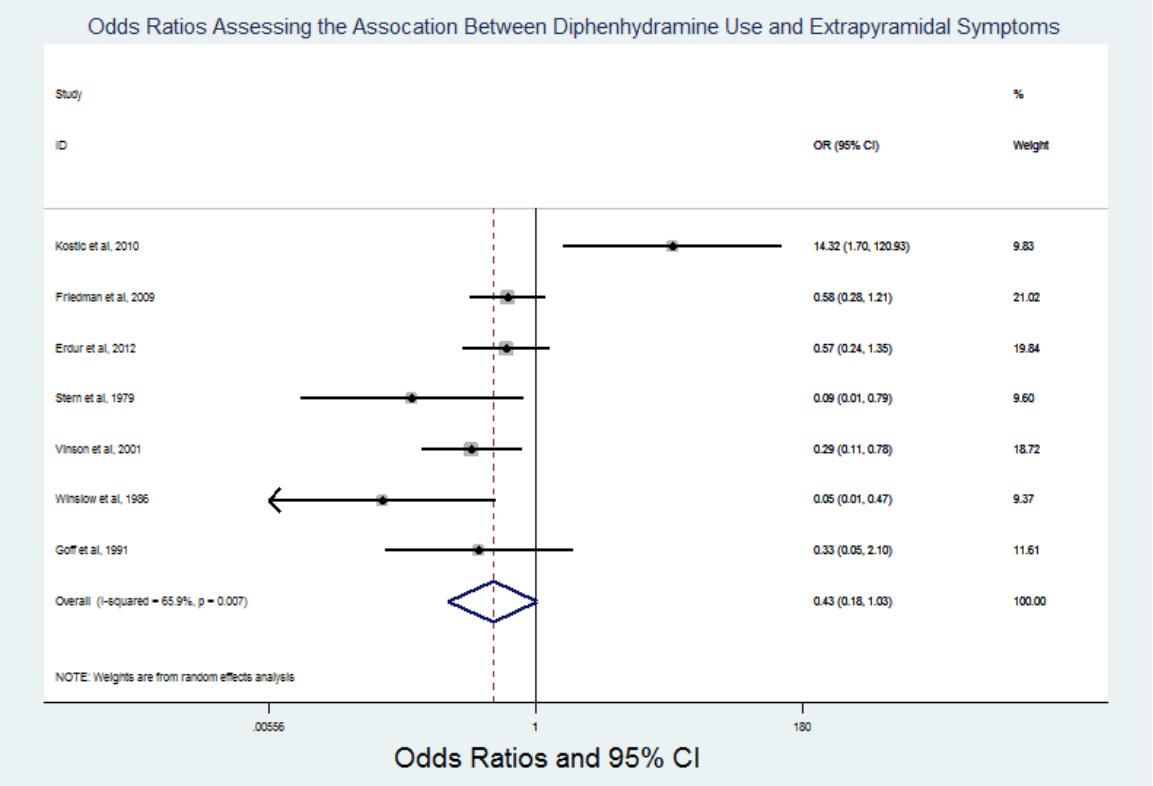

Figure 4. This figure demonstrates that utilization of diphenhydramine, as an adjunct medication in the prevention of EPS is significant. With an odds ratio of 0.43 there is a 57% overall reduction of risk by utilizing diphenhydramine adjunctively.

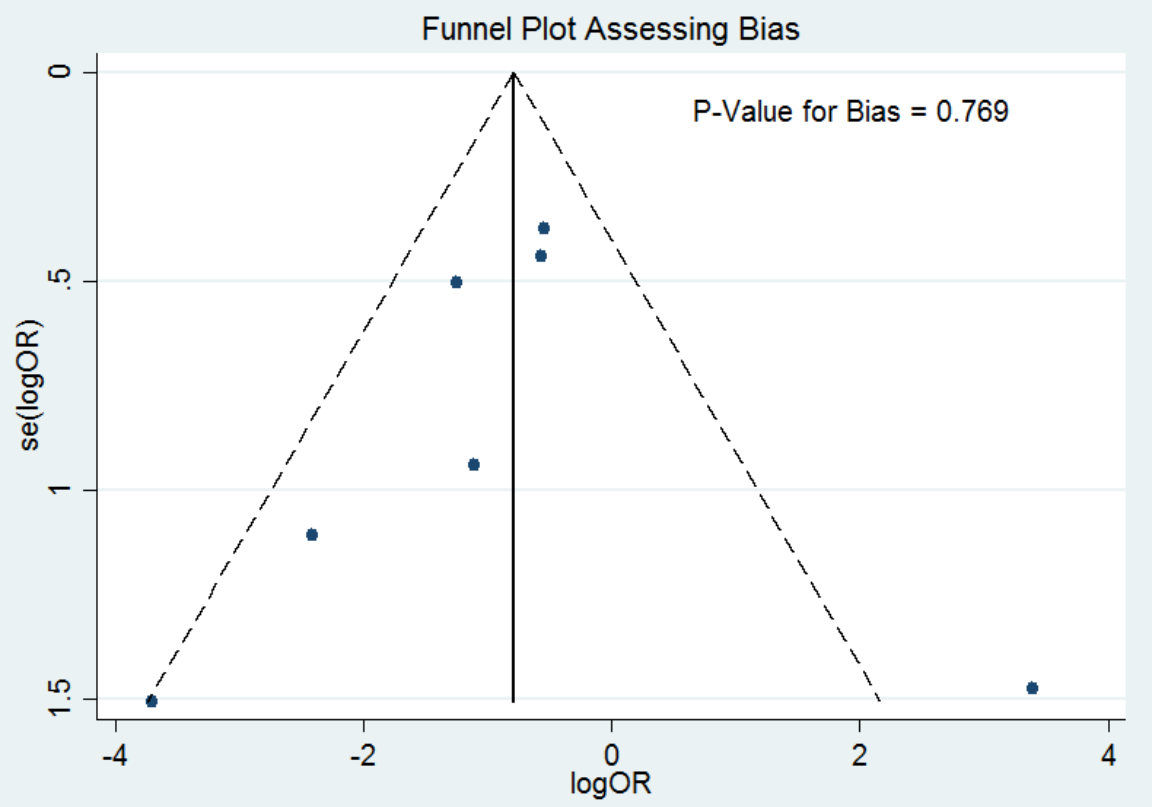

Figure 5. This figure demonstrates that publication bias in the studies utilized in this review is negligible.

Discussion & Conclusions

In this systematic review the authors found that anticholinergic adjuvant treatment prevented acute dystonia induced by antipsychotic medications for 60 minutes after administration. However, the two available studies that analyzed patients after 60 minutes had opposing results. Thus, there is no evidence of a long-term effect (defined as greater than 60 minutes from administration) in prevention of EPS with adjunctive medications. In the 4 studies and evaluated akathisia and the 3 studies that evaluated dystonia, adjuvant anticholinergic treatment was effective in preventing dystonia but not akathisia.

The prevention of EPS with adjuvant medications like benztropine or diphenhydramine has important clinical implications. Antipsychotics, prochlorperazine and metoclopramide are highly effective in treating acute psychotic episodes and nausea, vomiting respectively. However, the development of EPS may limit the utility of these medications in an acute setting. Diphenhydramine and benztropine are low-cost, benign medications and coadministration with any of the aforementioned medications may prevent dissatisfaction and disrupted patient care that can be associated with EPS.

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ACUTE EXTRAPYRAMIDAL SYMPTOMS INDUCED BY PHARMACOLOGICAL TREATMENT: A COMPREHENSIVE REVIEW

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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I. Introduction

Extrapyramidal symptoms are a set of hyperkinetic movement disorders usually stemming from prolonged or acute use of neuroleptic medications or acute use of anti-dopaminergic agents, such as metoclopramide, an anti-emetic. There are four primary groups of movement disorders include dystonia, dyskinesia, akathisia and Antipsychotic-induced Parkinsonism.

Dystonia is a grouping of sustained abnormal or involuntary muscle movements.[1] These movements can stem from various pathological states like Wilson's Disease or be pharmacologically induced. Symptom onset is varied, however onset can begin as quickly as minutes after a drug is administered. Dyskinesia is described as an abnormality of voluntary movements exemplified by from tardive dyskinesia occurring from long-term antipsychotic use. Antipsychotic-induced Parkinsonism includes the classic triad of rigidity, bradykinesia and rigidity with symptoms developing weeks into treatment. Akathisia is a sensation of restlessness and the perceived need for movement. It is often associated with use of neuroleptic medications and develops within minutes to hours.[2] For the purposes of this review, acute EPS, namely akathisia and dystonia were examined.

Electrophysiologically, dystonia is distinguished by a sustained, simultaneous contraction of agonist and antagonist muscles. Electrophysiological and imaging findings display loss of reflex inhibition in both spinal and brainstem reflexes as well as a loss of inhibitory patterns in the motor cortex. There is also evidence of sensory processing abnormalities. Slight impairment in temporal and spatial discrimination tasks, as well as somatosensory-evoked potentials is also observed.[3]

Similarly a study tremographically investigated six patients with akathisia.[4] The researchers placed accelerometers on the subjects hands an feet. They found patients with akathisia were characterized as having involuntary, large amplitude, low frequency (defined as less than 4 Hz), irregular but rhythmic foot movements.

Drugs used in emergency setting have the potential to produce acute EPS, such as dystonia and akathisia. Neuroleptics are used to treat acute psychotic episodes, as well as delirium and when sedation is desired for patient management. Metoclopramide is used to treat nausea and vomiting.

A proposed mechanism of action for the extrapyramidal effects of haloperidol and metoclopramide is that they bind and antagonize D2 receptors. The effect is so strong that >80% of the D2 receptor stimulation is decreased. It should be noted that there are several drugs that do not bind D2 receptors (SSRIs) are known to cause EPS. It is suggested that their mechanism of action involves direct stimulation of 5-HT_{2A} receptors.[5]

II. Scope of the Issue

The incidence and prevalence of acute drug-induced akathisia and dystonia is difficult to estimate due misdiagnosis, underreporting, and the lack of definitive diagnostic criteria.[6] This estimate includes all spectrums of akathisia induced by antipsychotics, anti-emetics and antidepressants in various settings. These reactions are more common in children, young adults and adolescents.[7]

III. Etiology

The pathophysiology of EPS is incompletely understood but the working hypothesis is that the symptoms occur due to antipsychotic-induced dopamine receptor (D2) occupancy above a threshold of 80%.[8] Cholinergic and adrenergic pathways may play a major role in regulation of symptoms.[8]

The goal of treatment when a neuroleptic is given is typically to block hyperactive dopamine neurons in the mesolimbic dopamine pathway. However, unintentional blockade of the Nigrostriatal pathway can occur as evidenced by massively increased risk of developing EPS following neuroleptic administration. Thus, D2 blockade is not limited to the Mesolimbic pathway.

The Nigrostriatal pathway connects the substantia nigra with the striatum and is principally implicated in movement. Loss of dopamine neurons in the substantia nigra is the principal driver behind the symptoms of Parkinson's disease, with progression of symptoms most apparent once 80-90% of the neurons have been lost. Thus, when a significant number of D2 receptors are blocked in the Nigrostriatal dopamine pathway by D2 Blockers, various movement disorders, not dissimilar to Parkinson's disease may emerge[8].

The Nigrostriatal pathway is part of the extrapyramidal system, hence the term extrapyramidal symptoms. Other members of the extrapyramidal system include the basal ganglia, cerebellum and vestibular nuclei. The term extrapyramidal is used to distinguish its tracts from the tracts of the motor cortex that travel through medullary pyramids.

Anticholinergic medications are commonly utilized to prevent or treat emergence of EPS. This phenomenon is predicated on the reciprocal relationship of dopamine and acetylcholine in the Nigrostriatal pathway. Normally, dopamine suppresses acetylcholine activity, thus removal of dopamine inhibition will lead to increased acetylcholine activity. If D2 receptors on the

cholinergic dendrite are blocked, acetylcholine will become overly active, resulting in production of EPS. Thus, the proposed pharmacological mechanism of EPS seems to be a relative dopamine deficiency and relative acetylcholine excess. Typical anti-psychotics with weak, inherent anticholinergic properties pose a risk of causing EPS. Conversely, those typical antipsychotics with greater anticholinergic properties will exhibit fewer EPS. If anticholinergic medications (Benztropine, Diphenhydramine) are administered, then the relative acetylcholine excess and subsequent movement disorder is circumvented[3].

IV. Clinical Identification Scales

Diagnosis and measurement of acute EPS is often difficult as subjective feelings of restlessness can be attributed to anxiety and abnormal movement can be attributed to psychosis. To address this difficulty several scales of measurement were developed.

The Barnes Akathisia Scale is utilized for diagnosis of drug-induced akathisia[2]. This scale utilizes both the patient's subjective awareness of restlessness, distress and objective presence of akathisia. In addition to these two measurements a global clinical assessment of akathisia is also measured. Items are rated on a four point scale, with more severe symptoms garnering a higher score.

The Simpson Angus Scale is utilized to assess pseudoparkinsonism. Signs assessed are gait, elbow and wrist rigidity, tremor and others. SAS scores can range from 0 to 40, with a 0-4 rating for each sign.

The Abnormal Involuntary Movement Scale is a 12-item scale used to assess dyskinesia. Scores range from 0-42, related to severity of extremity, trunk, and facial movements. 12 items are assessed (10 scored 0-4 (higher more severe) and 2 scored yes or no. This scale mainly utilizes practitioner observation, though sometimes the patient is asked questions.

The Extrapyramidal Symptom Rating Scale was designed to assess all EPS. This scale utilizes a subjective questionnaire and an objective physical exam. It assesses 12 items

V. Treatment and Prevention

Pharmacologic Treatment

If symptoms suddenly develop, then a cautious dose reduction should be attempted first, though the patient must be closely monitored for symptom exacerbation.

Beta blockers have been found to be helpful for akathisia. Their effect is likely due to their pharmacological properties in that they are lipophilic and can cross the blood brain barrier and they act on beta-2 receptors[5]. Propranolol is most typically used. Lipinski et al.[9] conducted a study in which all 12 patients experiencing akathisia experienced significant improvement upon treatment with 30-80mg per day of propranolol. Adler et al. compared Propranolol (40-80mg/day) and Benzatropine (1.5-4.0mg/day) in the treatment of akathisia and found that propranolol was superior in the reduction of symptoms.[10]

Benzodiazepines are used to treat akathisia for a multitude of reasons.[5] This is because the level of anxiety influences various manifestations of akathisia. Gagrat et al. conducted a double-blind study comparing a single IV dose of 5mg diazepam versus 50mg diphenhydramine to treat akathisia. Diazepam treated patients did not fare as well as those given diphenhydramine, though the difference was not statistically significant[11].

The rationale for treatment of extrapyramidal symptoms with anticholinergic medications is detailed in the pharmacology section. It is widely accepted that anticholinergic medications like Benztropine and Diphenhydramine are utilized when extrapyramidal symptoms occur. A small randomized controlled trial found Benztropine (1.5-4.0mg/day) to be effective in the emergence of akathisia[10]. A study by Fahn suggested that high-dose Trihexyphenidyl initially dosed at 5-6mg with a 2mg increase/wk up to 50mg, was effective in treating dystonia[12]. His study also suggested that anticholinergics may be more effective in treating EPS in children as

they can tolerate higher doses without experiencing severe anticholinergic side effects. Gagrat et al conducted a study that demonstrated improvement of akathisia and dystonia within 5 minutes of intravenous injection of 50mg of Diphenhydramine, with benefits persisting 2 hours after the initial injection[11]. However, it should be noted that the study was without a placebo control group.

Other medications have showed some promise in the treatment of EPS. Clonidine is an alpha-2 agonist that decreases central noradrenergic activity. One study utilized 0.05-0.20 mg/day of clonidine to treat 6 patients with neuroleptic induced EPS, of the six patients four of them experienced a decrease in symptoms[13].

Neuroleptic Selection in Prevention

First generation antipsychotics are therapeutic when 60-80% of the D2 receptors are occupied but when 75-80% of D2 receptors are occupied EPS emerge. Thus, an effective alternative with a decreased chance for EPS was desired.[14] Clozapine was the first Neuroleptic that was both effective and devoid of EPS.[15] However, the side effect profile of Clozapine, namely agranulocytosis made physicians cautious to utilize it. Even still, the utility of an antipsychotic with a decreased propensity to cause EPS served as motivation for the development of the second generation or "atypical" antipsychotics such as olanzapine, quetiaptine, ziprasidone, aripiprazole and risperidone.

These medications work similarly to the 1st generation antipsychotics in that they bind and antagonize the D2 receptor. Thought the mechanistic difference of 1st and 2nd generation antipsychotics is incompletely understood, one known difference is that most 2nd generation antipsychotics bind and antagonize the 5-HT_{2A} with near equal affinity as the binding on the D2 receptor. This has significant implications in that the 5-HT_{2A} receptor is a major regulator of the release of dopamine in the basal ganglia. Thus by blocking this receptor 2nd generation agents

increase dopamine release in the basal ganglia reducing the force of the D2 blockade the medication is initially causing.[16]

A competing theory to 5-HT2A antagonism is termed the "fast-off" theory.[17] This theory posits that the decreased incidence of EPS with 2nd generation antipsychotics is due to weak binding and fast dissociation of the medications to the D2 receptor site. Such that they bind only long enough to produce therapeutic effect but not long enough to produce EPS.
It should be noted that 2nd generation antipsychotics are not without their own side effects. Though they are reported to have a lower incidence of EPS common side effects include weight gain and related metabolic effects, cataracts, sexual dysfunction, hyperprolactinemia, hypotension, sedation, cardiac effects and weight gain. These side effects should be considered on a case by case basis as they may be contraindicated in patients with uncontrolled diabetes, liver disease. In an emergent setting, QT prolongation, sedation and hypotension are particularly relevant to care.

Anticholinergic Prophylaxis

The authors of this review have conducted a recent systematic review with preliminary results suggesting that, compared with no adjuvant treatment, adjuvant anticholinergic treatment of EPS induced by antipsychotic medications has a significant effect in prevention of both akathisia and dystonia in an acute setting.

Prevention is preferred as motor and mental agitation of akathisia can negatively affect patient care and satisfaction. A prospective study demonstrated 8% of patients receiving intravenous Prochlorperazine developed severe akathisia compelling them to move about the emergency department disruptively**.**[18]

Results demonstrated that adjuvant treatment is indicated in an acute setting, defined as onset of symptoms within 60 minutes of administering the medication with known EP sequelae.

However, studies have not demonstrated a significant effect in long term (defined as greater than 60 minutes from administration) prevention of EPS with adjunctive medications.

The prevention of dystonia and akathisia with adjuvant medications like Benztropine or Diphenhydramine has importantly clinical implications. Antipsychotics, Prochlorperazine and Metoclopramide are highly effective in treating acute psychotic episodes and nausea, vomiting respectively. However, the development of EPS may limit the utility of these medications in an acute setting. Diphenhydramine and Benztropine are low-cost, benign medications and coadministration with any of the aforementioned medications may prevent dissatisfaction and disrupted patient care that can be associated with EPS.

Appendix 1

Extrapyramidal Rating Scales:

Extrapyramidal symptom rating scale (ESRS) (Chouinard) © 1979

In case of doubt score the lesser severity.

I. QUESTIONNAIRE : Parkinsonism, Akathisia, Dystonia and Dyskinesia. *In this questionnaire, take into account the verbal report of the patient on the following: 1) the duration of the symptom during the day; 2) the number of days where the symptom was present during the last week; and, 3) the evaluation of the intensity of the symptom by the patient.*

Enquire into the status of each symptom and rate accordingly

	Absent	Mild	Moderate	Severe	
1. Impression of slowness or weakness, difficulty in carrying out routine tasks	0	1	2	3	⌊⌋
2. Difficulty walking or with balance					
3. Stiffness, stiff posture	0	1	2	3	⌊⌋
4. Restless, nervous, unable to keep still	0	1	2	3	⌊⌋
5. Tremors, shaking	0	1	2	3	⌊⌋
6. Oculogyric crisis, abnormal sustained posture	0	1	2	3	⌊⌋
7. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips, face, extremities or trunk	0	1	2	3	⌊⌋

II. EXAMINATION: PARKINSONISM AND AKATHISIA

Items based on physical examinations for Parkinsonism.

	Occasional	Frequent	Constant or almost so				
1. Tremor							
None:	0			Right upper limb			⌊⌋
Borderline:	1			Left upper limb			⌊⌋
Small amplitude:	2	3	4	Right lower limb			⌊⌋
Moderate amplitude:	3	4	5	Left lower limb			⌊⌋
Large amplitude:	4	5	6	Head	⌊⌋	Jaw/Chin	⌊⌋
				Tongue	⌊⌋	Lips	⌊⌋
2. Bradykinesia	0:	normal					
	1:	global impression of slowness in movements					
	2:	definite slowness in movements					
	3:	very mild difficulty in initiating movements					⌊⌋
	4:	mild to moderate difficulty in initiating movements					
	5:	difficulty in starting or stopping any movement, or freezing on initiating voluntary act					
	6:	rare voluntary movement, almost completely immobile					
3. Gait & posture	0:	normal					
	1:	mild decrease of pendular arm movement					
	2:	moderate decrease of pendular arm movement, normal steps					
	3:	no pendular arm movement, head flexed, steps more or less normal					⌊⌋

	4:	stiff posture (neck, back) small step (shuffling gait)		
	5:	more marked, festination or freezing on turning		
	6:	triple flexion, barely able to walk		
4. Postural stability	0:	normal		
	1:	hesitation when pushed but no retropulsion		
	2:	retropulsion but recovers unaided		
	3:	exaggerated retropulsion without falling		⌊⌋
	4:	absence of postural response would fall if not caught by examiner		
	5:	unstable while standing, even without pushing		
	6:	unable to stand without assistance		⌊⌋
5. Rigidity	0:	normal muscle tone	Right upper limb	⌊⌋
	1:	very mild, barely perceptible	Left upper limb	⌊⌋
	2:	mild (some resistance to passive movements)	Right lower limb	⌊⌋
	3:	moderate (definite difficulty to move the limb)	Left lower limb	⌊⌋
	4:	moderately severe (moderate resistance but still easy to move limb)		
	5:	severe (marked resistance with definite difficulty to move the limb)		
	6:	extremely severe (limb nearly frozen)		

Items based on overall observation during examination for Parkinsonism.

6 . Expressive automatic movements (Facial mask / speech)	0:	normal		
	1:	very mild decrease in facial expressiveness		
	2:	mild decrease in facial expressiveness		
	3:	rare spontaneous smile, decrease blinking, voice slightly monotonous		⌊⌋
	4:	no spontaneous smile, staring gaze, low monotonous speech, mumbling		
	5:	marked facial mask, unable to frown, slurred speech		
	6:	extremely severe facial mask with unintelligible speech		
7 . Akathisia	0:	absent		
	1:	looks restless, nervous, impatient, uncomfortable		
	2:	needs to move at least one extremity		
	3:	often needs to move one extremity or to change position		⌊⌋

4:	moves one extremity almost constantly if sitting, or stamps feet while standing	
5:	unable to sit down for more than a short period of time	
6:	moves or walks constantly	

III. EXAMINATION: DYSTONIA

Based on examination and observation

Acute torsion, and non acute or chronic or tardive dystonia

0:	absent	Right upper limb			⌊_⌋
1:	very mild	Left upper limb			⌊_⌋
2:	mild	Right lower limb			⌊_⌋
3:	moderate	Left lower limb			⌊_⌋
4:	moderately severe	Head	⌊_⌋	Jaw/Chin	⌊_⌋
5:	severe	Tongue	⌊_⌋	Lips	⌊_⌋
6:	extremely severe	Eyes	⌊_⌋	Trunk	⌊_⌋

IV. EXAMINATION: DYSKINETIC MOVEMENT

Based on examination and observation

		Occasional*	Frequent**	Constant or almost so	
1. Lingual movements (slow lateral or torsion movement of tongue)					
none:	0				
borderline:	1				
clearly present, within oral cavity:		2	3	4	
with occasional partial protrusion:		3	4	5	
with complete protusion:		4	5	6	⌊_⌋
2. Jaw movements (lateral movement, chewing, biting clenching)					
none:	0				
borderline:	1				
clearly present, small amplitude:		2	3	4	
moderate amplitude: but without mouth opening:		3	4	5	
large amplitude: with mouth opening:		4	5	6	⌊_⌋
3. Bucco-labial movements (puckering, pouting, smacking, etc.)					
none:	0				
borderline:	1				
clearly present, small amplitude:		3	3	4	
moderate amplitude, forward movement of lips:		4	4	5	
large amplitude; marked, noisy smacking of lips:		5	5	6	⌊_⌋

4. Truncal movements (involuntary rocking, twisting, pelvic gyrations)
   - none: 0
   - borderline: 1
   - clearly present, small amplitude: 2
   - moderate amplitude: 3
   - greater amplitude: 4

5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)
   - none: 0
   - borderline: 1
   - clearly present, small amplitude, movement of one limb: 2
   - moderate amplitude, movement of one limb or movement of small amplitude involving two limbs: 3
   - greater amplitude, movement involving two limbs: 4

6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)
   - none: 0
   - borderline: 1
   - clearly present, small amplitude, movement of one limb: 2
   - moderate amplitude, movement of one limb or movement of small amplitude involving two limbs: 3
   - greater amplitude, movement involving two limbs: 4

7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.)
   - none: 0
   - borderline: 1
   - clearly present, small amplitude: 2
   - moderate amplitude: 3
   - greater amplitude: 4

Specify.....

* when activated or rarely spontaneous;

** frequently spontaneous and present when activated

V. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA

Considering your clinical experience, how severe is the dyskinesia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VI. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF PARKINSONISM

Considering your clinical experience, how severe is the parkinsonism at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSTONIA

Considering your clinical experience, how severe is the dystonia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

VIII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF AKATHISIA

Considering your clinical experience, how severe is the akathisia at this time?

0: absent	3: mild	6: marked
1: borderline	4: moderate	7: severe
2: very mild	5: moderately sever	8: extremely severe

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

NAME:_____
DATE: _____
Prescribing Practitioner: _____

CODE: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 - Severe

INSTRUCTIONS:
Complete Examination Procedure (attachment d.)
before making ratings

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date	RATER Date	RATER Date	RATER Date
Facial and Oral Movements	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows periorbital area, cheeks, including frowning blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g., puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw e.g. biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	O 1 2 3 4
Extremity Movements	**5. Upper (arms, wrists,, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Trunk Movements	**7. Neck, shoulders, hips** e.g., rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Global Judgments	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patient's report No awareness 0 Aware, no distress 1 Aware, mild distress 2 Aware, moderate distress 3 Aware, severe distress 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
Dental Status	**11. Current problems with teeth and/or dentures**	No Yes	No Yes	No Yes	No Yes
	12. Are dentures usually worn?	No Yes	No Yes	No Yes	No Yes
	13. Edentia?	No Yes	No Yes	No Yes	No Yes
	14. Do movements disappear in sleep?	No Yes	No Yes	No Yes	No Yes

Final: 9/2000

Patient Name:_____ Date: _____

SIMPSON-ANGUS EXTRAPYRAMIDAL SIDE EFFECTS SCALE

The exam should be conducted in a room where the subject can walk a sufficient distance to allow him/her to get into a natural rhythm (e.g. 15 paces). Each side of the body should be examined. If one side shows more pronounced pathology than the other, this score should be noted and this taken. Cogwheel rigidity may be palpated when the examination is carried out for items 3, 4, 5, and 6. It is not rated separately and Is merely another way to detect rigidity. It would indicate that a minimum score of 1 would be mandatory.

1. **Gait**: The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:
   - 0 Normal
   - 1 Diminution in swing while the patient is walking
   - 2 Marked diminution in swing with obvious rigidity in the arm
   - 3 Stiff gait with arms held rigidly before the abdomen
   - 4 Stooped shuffling gait with propulsion and retropulsion

2. **Arm Dropping:** The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:
   - 0 Normal, free fall with loud slap and rebound
   - 1 Fall slowed slightly with less audible contact and little rebound
   - 2 Fall slowed, no rebound
   - 3 Marked slowing, no slap at all
   - 4 Arms fall as though against resistance; as though through glue

3. **Shoulder Shaking:** The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The subject's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:
   - 0 Normal
   - 1 Slight stiffness and resistance
   - 2 Moderate stiffness and resistance
   - 3 Marked rigidity with difficulty in passive movement
   - 4 Extreme stiffness and rigidity with almost a frozen shoulder

4. **Elbow Rigidity:** The elbow joints are separately bent at right angles and passively extended and flexed, with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)
   - 0 Normal
   - 1 Slight stiffness and resistance
   - 2 Moderate stiffness and resistance
   - 3 Marked rigidity with difficulty in passive movement
   - 4 Extreme stiffness and rigidity with almost a frozen elbow

5. **Wrist Rigidity or Fixation of Position:** The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulnar and radial deviation:
   - 0 Normal
   - 1 Slight stiffness and resistance
   - 2 Moderate stiffness and resistance
   - 3 Marked rigidity with difficulty in passive movement
   - 4 Extreme stiffness and rigidity with almost frozen wrist

6. **Leg Pendulousness:** The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:
   - 0 The legs swing freely
   - 1 Slight diminution in the swing of the legs
   - 2 Moderate resistance to swing
   - 3 Marked resistance and damping of swing
   - 4 Complete absence of swing

7. **Head Dropping:** The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal subject the head will fall upon the table. The movement is delayed in extrapyramidal system disorder, and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:
   - 0 The head falls completely with a good thump as it hits the table
   - 1 Slight slowing in fall, mainly noted by lack of slap as head meets the table
   - 2 Moderate slowing in the fall quite noticeable to the eye
   - 3 Head falls stiffly and slowly
   - 4 Head does not reach the examining table

8. **Glabella Tap**: Subject is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:
   - 0 0-5 blinks
   - 1 6-10 blinks
   - 2 11-15 blinks
   - 3 16-20 blinks
   - 4 21 and more blinks

9. **Tremor:** Patient is observed walking into examining room and is then reexamined for this item:
   - 0 Normal
   - 1 Mild finger tremor, obvious to sight and touch
   - 2 Tremor of hand or arm occurring spasmodically
   - 3 Persistent tremor of one or more limbs
   - 4 Whole body tremor

10. **Salivation:** Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:
    - 0 Normal
    - 1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
    - 2 When excess salivation is present and might occasionally result in difficulty speaking
    - 3 Speaking with difficulty because of excess salivation
    - 4 Frank drooling

Name:_____ **Date:**_____

Barnes Akathisia Rating Scale (BARS)

Instructions: Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, *and/or* rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, *and/or* has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness
0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, *and/or* complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time *and/or* reports strong desire to walk or pace most of the time

Distress related to restlessness
0 No distress
1 Mild
2 Moderate
3 Severe

Global Clinical Assessment of Akathisia

0 *Absent.* No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 *Questionable.* Non-specific inner tension and fidgety movements
2 *Mild akathisia.* Awareness of restlessness in the legs *and/or* inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.
3 *Moderate akathisia.* Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4 *Marked akathisia.* Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.
5 *Severe akathisia.* The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia.

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