

Should Anticholinergic Drugs Be Used for Neuroleptic-Induced Acute Akathisia?

EBEM Commentator Contact

Adam Koertner, MD

From the Department of Emergency Medicine, San Antonio Uniformed Services Health Education Consortium, San Antonio, TX.

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Rathbone J, Soares-Weiser K. Anticholinergics for neuroleptic-induced acute akathisia. *Cochrane Database Syst Rev.* 2006;4:CD003727.

The *Annals'* EBEM editor assisted in the preparation of the abstract of this Cochrane systematic review, as well as selection of the "Evidence-Based Medicine Teaching Points."

OBJECTIVE

To determine whether anticholinergic drugs are effective compared to placebo for treatment of neuroleptic-induced acute akathisia. A secondary objective was to determine the effects of anticholinergic drugs for akathisia according to previous psychiatric diagnoses (ie, schizophrenia and psychosis versus mood disorders, versus other).

DATA SOURCES

The authors searched Biological Abstracts (1982 to 1999), CINAHL (1982 to 1999), Cochrane Library (Issue 4, 1999), Cochrane Schizophrenia Group's Register (October 1999), EMBASE (1980 to 1999), LILACS (1982 to 1999), MEDLINE (1966 to 1999), PsycLIT (1974 to 1999), and Cochrane Schizophrenia Group's Register (July 2005). First authors were contacted and background trials were sought in the References sections of all included trials. The review was initially performed in 2002, with a major update in 2005 and a minor update in 2006.

STUDY SELECTION

Trials were included if they were randomized placebo-controlled trials of anticholinergic drugs for people with neuroleptic-induced acute akathisia; quasirandomized and crossover trials without first-period data were excluded. The

search strategy was not limited by previous psychiatric diagnoses, age, sex, or diagnostic criteria.

Anticholinergic drugs included in the review were benzhexol, benztropine, biperiden, dextimide, orphenadrine, procyclidine, scopolamine, or trihexyphenidyl. Trials were included irrespective of dose or route of administration. Trials comparing active treatment groups were not included in the review.

Outcome measures included akathisia symptoms, general mental state changes, acceptability and tolerability of treatment, and adverse events. Outcomes were identified in predetermined time courses of short term (<6 weeks), medium term (6 weeks to 6 months), and long term (>6 months).

DATA EXTRACTION AND ANALYSIS

The reviewers independently determined inclusion; disagreement was resolved with discussion and further information from source authors. The reviewers measured interrater reliability of agreement for inclusion criteria using the weighted κ coefficient. Quality assessment of the individual trials was planned using Cochrane Handbook criteria and the Jadad scale, with inclusion criteria of low to moderate risk of bias per Cochrane criteria.

MAIN RESULTS

The search strategies identified 1,350 potential citations, of which 11 studies involved the use of anticholinergic treatment. Trials were excluded because of methodologic weaknesses or confounding medications. As a result, the review failed to identify any randomized trials of anticholinergic drugs for neuroleptic-induced acute akathisia.

CONCLUSIONS

There is a lack of good evidence to support or refute the use of anticholinergic medications for treatment of neuroleptic-induced acute akathisia.

Cochrane Systematic Review Author Contact

John Rathbone, BSc, MPhil

Department of Psychiatry

The University of Leeds

E-mail: jrathbone@cochrane-sz.org

COMMENTARY: CLINICAL IMPLICATION

Akathisia is a common and concerning adverse effect of neuroleptic medications. Akathisia presents as a spectrum of symptoms from restless legs to anxiety, with severity ranging from subjective restlessness to acute agitation. Studies of individual neuroleptic medications have found the incidence of akathisia to range between 10% and 80%, with a conservative estimate of approximately 30%.^{1,2} A variety of medications may cause akathisia, and many are frequently used in the emergency department (ED). These include prochlorperazine, promethazine, droperidol, haloperidol, and metoclopramide, which are commonly used for nausea and migraine treatment in the ED. The true incidence of akathisia in the ED is unknown; however, it is believed to be significantly underdiagnosed. Unless patients have a severe presentation or their symptoms are specifically monitored or sought, akathisia is likely to go unnoticed by caregivers.

Potential adverse effects of akathisia include decreased patient satisfaction, physical or pharmacological restraint, increased use of medical resources, incomplete evaluation and treatment, and limitations of future therapeutic options when the patient claims the reaction is an "allergy."³⁻⁷

Treatment of akathisia is largely based on observational evidence. There are currently no evidence-based guidelines on its treatment. This high-quality Cochrane review used stringent yet reasonable inclusion criteria and failed to find sufficient data about the use of anticholinergic medications for treatment of neuroleptic-induced acute akathisia. Of note, this review did not include the antihistamine diphenhydramine, which also has anticholinergic effects and demonstrated promising results in a randomized, placebo-controlled prevention (not treatment) trial.⁸ In addition, comparative trials were not included, which limited the scope of the review.

TAKE-HOME MESSAGE

There is a paucity of high-quality data on the use of anticholinergic drugs for treatment of neuroleptic-induced acute akathisia. Current use of anticholinergic drugs for akathisia is based largely on observational evidence and open-label or poorly controlled trials. More studies are needed to define the role of these agents for treatment of this distressing and frequently encountered condition. In the meantime, akathisia treatment options for emergency physician include diphenhydramine or benzodiazepines. In addition, akathisia may be prevented by administering diphenhydramine, along with neuroleptic medications.

EBEM Commentator Contact

Adam Koertner, MD

Department of Emergency Medicine

San Antonio Uniformed Services Health Education Consortium

E-mail adam.koertner@lackland.af.mil

EBEM TEACHING POINT

Crossover trials and carryover effects. Crossover trials are clinical experiments in which individual patients are subjected to 2 or more interventions. Patients are ideally randomly assigned to a particular treatment (A or B) for a specified period, followed by a treatment-free time (washout period), after which the patients are given the alternative treatment (B or A). Patients and investigators may be blinded to the specific treatments and the specific point at which the crossover occurs. The effects of the interventions are then compared and contrasted individually. Crossover trials are attractive to investigators because they diminish the necessary sample size and limit confounding variables by having patients serving as their own comparator.⁹

Crossover trials have several important limitations. First, patients must be recruited with diseases that are stable (ie, not during an exacerbation). Second, the outcome cannot terminate the trial during one of the treatment periods (eg, a crossover trial of treatment for infertility is terminated with a pregnancy). Third, the design should consider possible intervention carryover effects. The carryover effect refers to residual effects of one treatment that may positively or negatively influence the later treatment. Researchers aim to minimize the carryover effect by providing a washout period between interventions. In drug trials, the duration of the washout period is typically based on pharmacokinetic properties of the involved medications. A period of 4 or 5 half-lives is believed by many to be adequate time for washout of a particular substance, correlating to a 94% and 97% reduction in serum concentrations, respectively. It is possible, however, that carryover effects occur independent of a drug's serum concentration. An example would be the development of tardive dyskinesia during first-period treatment with a neuroleptic. If the tardive dyskinesia persisted beyond the washout into the second-period treatment, it would affect the analysis of the later treatment period.

Results of crossover trials must be interpreted after acceptance of the assumption that carryover has not occurred or that the likelihood of carryover is low. If carryover is thought to have occurred, it is customary to analyze only the data from the first treatment period, as suggested in the *Cochrane Handbook* 8.11.3.3 and *Methods* section of the Cochrane review which is the source of this abstract. This action will negate any intended benefit of the crossover design but may be the only reliable way to salvage what would otherwise be viewed as questionable results.

REFERENCES

1. Ball R. Drug-induced akathisia: a review. *J R Soc Med.* 1985;78:748-752.
2. Braude D, Soliz T, Crandall C, et al. Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. *Am J Emerg Med.* 2006;24:177-182.
3. Dauner A, Blair DT. Akathisia. When treatment creates a problem. *J Psychosoc Nurs Ment Health Serv.* 1990;28:13-18.

4. Rodgers C. Extrapyramidal side effects of antiemetics presenting as psychiatric illness. *Gen Hosp Psychiatry*. 1992;14:192-195.
5. Braude D, Boling S. Case report of unrecognized akathisia resulting in an emergency landing and RSI during air medical transport. *Air Med J*. 2006;25:85-87.
6. LaGorio J, Thompson VA, Sternberg D, et al. Akathisia and anesthesia: refusal of surgery after the administration of metoclopramide. *Anesth Analg*. 1998;87:224-227.
7. Poortinga E, Rosenthal D, Bagri S. Metoclopramide-induced akathisia during the second trimester of a 37-year-old woman's first pregnancy. *Psychosomatics*. 2001;42:153-156.
8. Vinson DR, Drotts DL. Diphenhydramine for the prevention of akathisia induced by prochlorperazine: a randomized, controlled trial. *Ann Emerg Med*. 2001;37:125-131.
9. Louis TA, Lavori PW, Bailar JC 3rd, et al. Crossover and self-controlled designs in clinical research. *N Engl J Med*. 1984;310:24-31.