

Clothiapine for acute psychotic illness: a meta-analysis

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ABSTRACT

Objectives: To estimate the effects of clothiapine, a dibenzothiazepine neuroleptic, for the management of acute psychosis. **Methods:** Six databases were searched, reference lists were inspected and relevant industry and authors contacted. Randomised clinical trials involving clothiapine for acute psychosis were identified and relevant data extracted. **Results:** Five relevant trials were found comparing clothiapine with antipsychotics or lorazepam. We found no evidence to support or refute the use of clothiapine in the psychiatric emergency (no significant improvement compared with other antipsychotics RR 0.82, 95% CI 0.2 to 3.1, heterogeneous $p=0.09$, $N=83$; no difference in mental state change when clothiapine was compared to lorazepam WMD -3.36 95%CI -8.09 to 1.37, $N=60$). Clothiapine may result in less need for antiparkinsonian treatment than zuclopenthixol acetate (RR 0.43, 95%CI 0.02 to 0.98, $N=38$). **Conclusions:** Wide confidence intervals prevent any firm conclusions, but clothiapine could be effective and cheap for rapid tranquillisation.

Keywords: Clothiapine; Acute Psychosis; Neuroleptic Drugs; Tranquillizing Drugs; Meta-analysis

Introduction

Acute psychosis requires psychological and pharmacological treatment and, when a risk of self-harm or harm to others is present, the need for treatment can become urgent. Ideally, the drug(s) used in urgent treatment of acute psychosis should have a swift onset of effect, good tranquillizing or sedative properties, antipsychotic action, and minimal or no adverse effects. Various drug regimens are used in the emergency situation but guidelines^{1,2,3} and clinical practice vary.^{4,5}

Clothiapine, 2-chloro-11-(4-methyl-1-piperazinyl)dibenzo[b,f][1,4]thiazepine, is a dibenzothiazepine neuroleptic which has general properties similar to those of the phenothiazines, such as chlorpromazine, but a chemical structure, and perhaps properties, similar to clozapine.⁶ Indeed, as is the case for this atypical antipsychotic, clotiapine downregulates cortical 5HT₂-receptors, blocks 5HT₃-receptors and has been shown to have high affinity for 5-HT₆ and 5-HT₇ receptors. In the rat retinal model, this drug seems to act as an antagonist of the D₄-receptor and its ratio of D₂ to 5HT₂ blockade is similar to that of clozapine.⁶ Clotiapine (Clothiapine, Clotiapina, Entumin(e), Etumine, Etomina,

Etomin) has been used in the acute psychiatric emergency since the late 1960s when it was put on the market by Wander Laboratories (now Novartis Pharma). It is an antipsychotic with a rapid onset of action and a strong sedative effect, said to be comparable to that of zuclopenthixol acetate with fewer extrapyramidal side-effects.⁷ Clotiapine is defined by some sources as an atypical neuroleptic.^{8,9} This definition is not widespread, but would certainly fit clotiapine's receptor-affinity profile and possibly also its low rates of extrapyramidal side-effects.⁷ In the few studies published on this drug we found no means of invalidating this hypothesis and we believe it is one worthy of consideration.

Clotiapine is used in Argentina, Belgium, Israel, Italy, Luxembourg, South Africa, Spain, Switzerland and Taiwan. A survey of the drugs prescribed in a Swiss psychiatric university hospital found it to be among the three most prescribed psychotropics in this particular establishment.¹⁰ The manufacturing company, state clotiapine to be indicated for the management of acute or exacerbations of chronic schizophrenia, chronic schizophrenia, bipolar disorder especially mania, other forms of acute psychotic illness, agitation of endogenous or exogenous (drugs, alcohol) cause, panic, inner uneasiness, drug withdrawal symptoms, states of depersonalisation, hyperactivity and sleep disorder. Data on the extent of its use have not been possible to find. There is an oral form (40mg) and injectable clotiapine (10mg) is available for intra-muscular (IM) or intravenous (IV) use. The dosage for acute psychosis is usu-

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ally between 120 and 200mg/day, but can be as high as 360mg/day. Currently, the cost of medication with clotiapine in Switzerland is of 0.55 Swiss Francs (~ £0.20) for one oral dose (40mg). The injectable form has been taken off the Swiss market last year for non-clinical reasons.

Our objective was to estimate the effects of clotiapine, including its cost-effectiveness, when compared to other 'standard' or 'non-standard' treatments of acute psychotic illness, in controlling disturbed behaviour and reducing psychotic symptoms.

Experimental Procedures

Criteria

Studies included were randomised clinical trials involving clotiapine for people with acute psychotic illnesses such as in schizophrenia, schizoaffective disorder, mixed affective disorders, manic phase of bipolar disorder, brief psychotic episode or organic psychosis following substance abuse. For the purposes of this review, 'acute' was pre-defined as where authors of trials refer to the majority of participants as experiencing an 'acute illness/relapse/exacerbation' or phrases that imply that positive symptoms of the illness (such as delusions, hallucinations, formal thought disorders, motor hyperactivity) have recently appeared or shown exacerbation.

Searches

The Cochrane Controlled Trials Register (Issue 2, 2000), The Cochrane Schizophrenia Group's Register (May 2000), EMBASE (1980-2000), MEDLINE (1966-2000), PASCAL (1973-2000) and PsycLIT (1970-2000) were methodically searched (see Cochrane Review for full details). Reference lists of included and excluded studies were also searched and the Medical Information Centre of the manufacturing company was contacted for additional trials. Authors of relevant studies were also contacted.

Data extraction and assimilation

Studies were reliably selected, quality assessed and data extracted.¹² For binary outcomes a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI) was calculated. For continuous outcomes, endpoint data were preferred to change data. If heterogeneity was found, a random effects model was used and reasons for heterogeneity investigated.

Results

470 citations were found. Thirty-five citations referred to trials using clotiapine but most were case series, and therefore excluded. Five trials were included in our meta-analysis (Table 1).^{7,13,14,15,16}

The participants were adults with schizophrenia, 'paranoid schizophrenia' or people suffering from 'psychosis'. All were said to be 'acutely' ill or 'in a state of intense excitement' (total N=185) and all trials were conducted in hospital. No randomised trials compared clotiapine with placebo, but with oral perphenazine (12-64mg/day), oral chlorpromazine (100-600mg/day), trifluoperazine both IM (2-8mg/day) and orally (10-40mg/day), lorazepam IM (up to 16mg/day), and finally zuclopenthixol acetate (150mg/72 hours) (Table 1). Trials lasted between six and sixty days, but only two studies measured outcomes at 24 hours or less, thus presenting some data on clotiapine's speed of action.

All trials were poorly reported. For clinical outcomes, data were mostly continuous, presented as mean values, commonly

without standard deviations (SD). Some were presented in graphical form only. Two trials measured outcomes at 24 hours or less but no data could be included in the meta-analysis.^{7,13} Sedation was measured in one study at two, four, eight and twenty-four hours after an injection of clotiapine or zuclopenthixol acetate.⁷ The authors, however, did not present data, merely stating that both drugs rapidly induced sedation, which peaked at eight hours. The same study measured clinical effects and adverse events using four scales at twenty-four hours. Again, no data were reported. Jacobsson, measured modification of behaviour (Wing rating scale), and concluded that both clotiapine and chlorpromazine produced a significant improvement at one month, but no data were presented.¹⁶ Subramaney, comparing clotiapine IM with lorazepam IM also measured change in behaviour (Overt Aggression Scale), and quantified side effects (Sirason-Angus Scale) at 24 hours.^{13,17,18} These results could not be used as data were skewed, but the trialists found clotiapine to be as effective as lorazepam for the control of aggressive behaviour, although the latter drug produced less adverse events. No trial comparing clotiapine with other antipsychotics reported usable data on effects on mental state. Other outcome measurements used were: categorical scales measuring degrees of clinical improvement as defined by the study, number of people needing antiparkinsonian medication or quantity of antiparkinsonian drugs used and number of people substantially improved and discharged before the end of the trial. Economic outcomes and satisfaction with care were not addressed in any of the trials.

Three studies reported usable data on the clinical improvement of patients treated with clotiapine compared to other antipsychotics.^{14,15,16} Two studies were administering drugs orally and used a low potency neuroleptic as a comparison, whereas another compared clotiapine IM to IM trifluoperazine - a high potency neuroleptic.¹⁵ Unsurprisingly, pooled results were heterogeneous ($p=0.09$), even when a random effects model was employed (no significant improvement at 30, 45 and 60 days RR 0.82 95% CI 0.2 to 3.1, heterogeneous $p=0.09$, $N=83$). In any event, small sample sizes and the resulting wide confidence intervals preclude firm conclusions. Only one small ($n=49$) trial addressed the issue of hospital discharge due to substantial improvement.¹⁶ The result was similar for clotiapine and chlorpromazine (unable to be discharged by 1 month RR 1.04 CI 0.96 to 1.12, $N=49$). Overall, there was no discernable difference in the number of people leaving the studies early from each group (17% vs 8%, RR 2.3 CI 0.4 to 13, $N=121$). In one of the studies, two people were excluded from the trial because of severe adverse effects; one person left early as he was 'cured' and eight people's condition deteriorated and they had to be given other medication.¹⁶

Several scales were used for quantifying side effects (Table 1), but results could not be pooled as insufficient data were reported. Two trials measured the quantity of antiparkinsonian drugs used to control involuntary movements. One found no significant difference between clotiapine and chlorpromazine (RR 0.92 CI 0.52 to 1.47)¹⁶, whereas in Uys⁷, zuclopenthixol acetate provoked more movement disorders and therefore required more antiparkinsonian treatment than clotiapine (RR 0.11 CI 0.02 to 0.8). Heterogeneity of data prevented pooling of these results.

One small ($N=60$) trial used a benzodiazepine as the drug of comparison for the management of episodes of acute agitation

in psychotic patients receiving haloperidol as a baseline treatment.¹³ Clotiapine was slightly, but not significantly, more effective than lorazepam in improving the mental state at one week (MD -3.4 CI -8.1 to 1.4), as measured by the Brief Psychiatric Rating Scale.¹⁹ One participant in each treatment group

dropped out before the end of the trial (RR 1.00 CI 0.07 to 15.26). The trialists applied the Overt Aggression Scale to measure the level of aggression in participants.¹⁷ At 24 hours there was no difference between groups (clotiapine mean 1.33 SD 2.78, n=30, lorazepam mean 1.83 SD 3.14, n=30).

Table 1

Study	Methods	Participants	Interventions	Outcomes
Itoh et al 1968 ¹⁴	Allocation: matched pairs, randomised, table of random numbers. Blinding: double. Duration: 60 days (preceded by 1 week washout).	Diagnosis: schizophrenia (criteria not mentioned). History: 4 in 'state of intense excitement' - possible to extract data on only these people. N=80 (4 included). Sex: 62 M, 18 F. Age: mean ~34 years. Setting: hospital.	1. Clotiapine: dose 45 to 90mg/day orally by day 7, as needed thereafter, range 90-290mg/day. N=2. 2. Perphenazine: dose 12-24mg/day orally by day 7, as needed thereafter, range 24-64mg/day. N=2.	General improvement: overall clinical response. Unable to use - Mental state: PRSS. Side-effects. Leaving the study early.
Jacobsson et al 1974 ¹⁶	Allocation: randomised, pre-established code. Blinding: double. Duration: one month (preceded by 'a few days' washout).	Diagnosis: 'psychotic syndromes of a schizophrenic type'. History: acute, first episode or relapse. N=49. Sex: 23 M, 26 F. Age: range 18-60 years. Setting: hospital.	1. Clotiapine: dose 40-240mg/day orally. N=23. 2. Chlorpromazine: dose 100-600mg/day orally. N=26.	General improvement: overall clinical response. Side-effects: needing antiparkinsonian treatment. Leaving study early. Unable to use - Behaviour: Wing Rating Scale for Ward Behaviour. Mental state: Authors' modification of the 'Martens & Jonsson' Symptom. Side-effects: Scale for Rating of Side-Effects.
Perales et al 1974 ¹⁵	Allocation: randomised, table of random numbers. Blinding: double (but likely that oral doses of drugs caused unblinding). Duration: 45 days.	Diagnosis: paranoide schizophrenia. History: acute. N=30. Sex: 26 M, 4 F. Age: range 19-43 years. Setting: hospital.	1. Clotiapine: dose 40-160mg/day IM from day 1-5, then 40-160mg/day orally until the end of trial. N=15. 2. Trifluoperazine: dose 2-8mg/day IM from day one to day five, then 10-40mg/day orally until the end of trial. N=15.	Global improvement: degree of improvement on categorical scale. Side-effects: list of adverse effects. Leaving study early. Unable to use - Mental state: BPRS. Side-effects: Bordelau's Extrapyramidal Symptoms Scale, use of antiparkinsonian drugs.
Subramanyam Brook et al 1998 ¹³	Allocation: randomised - by toss of a coin. Blinding: double. Duration: one week.	Diagnosis: organic (psychoactive substance) hallucinosis, organic delusional disorder, schizophrenia, bipolar disorder (DSM III). History: acutely behaviourally disturbed with aggressive, disorganised behaviour. N=60. Sex: 46 M, 14 F. Age: range 18-45 years. Setting: hospital.	1. Clotiapine: maximum dose 40mg IM 6 hourly + haloperidol 10mg/day orally. N=30. 2. Lorazepam: maximum dose 4mg IM 6 hourly + haloperidol 10mg/day orally. N=30.	Mental state: BPRS. Leaving study early. Unable to use - Behaviour: Overt Aggression Scale. Side-effects: Simpson-Angus Scale.
Uys et al 1996 ⁷	Allocation: randomised - by toss of a coin. Blinding: double. Duration: one week.	Diagnosis: schizophrenia, acute paranoid reaction, other and unspecific reactive psychosis, unspecified psychosis, bipolar mood disorder-manic phase (ICD 9). History: acute restless or aggressive behaviour. N=42. Sex: 42 M. Age: range 18-65 years. Setting: hospital.	1. Clotiapine: dose 40mg IM initially, then 80-160mg/day, in divided doses, orally or IM. N=21. 2. Zuclopenthixol acetate: dose 150mg IM initially, repeated once after 72 hours. N=21.	Side-effects: needing anticholinergic medication, frequent side-effects, pain at site of injection. Leaving the study early. Unable to use - General improvement: CGI. Sedation: Likert Scale. Mental state: BPRS, Bech Rafaelsen Mania Rating Scale. Side-effects: reduced UKU Side-Effect Rating Scale.

Discussion

We found few controlled clinical trials using clotiapipe for the management of acute psychotic illness and very few since the mid 1970s, probably following its disappearance from the market in France, the UK and USA. The reason given by Novartis for the withdrawal was that it was not economical to market an off-patent compound. The included trials were mostly small and poorly reported. Results were made difficult to compare by the facts that each trial used a different control drug - either a high potency neuroleptic (trifluoperazine, zuclopenthixol acetate), a low potency neuroleptic (chlorpromazine, perphenazine) or a benzodiazepine - and wide ranges of drug doses were used, sometimes well above recommended dosages (this was the case for trifluoperazine and chlorpromazine). This review on the effectiveness of clotiapipe for the management of acute psychosis leaves many questions unanswered. Satisfaction with care as well as economic issues were not addressed. It would also have been interesting to know whether treatment with clotiapipe can help prevent hospitalisation for acutely psychotic individuals, but no trial was conducted in the community. However, the value of this interesting and inexpensive compound has not been disproved. With the advent of expensive preparations of atypical antipsychotics for rapid tranquillisation, it is important to fully evaluate all available treatments.^{20,21,22} Comparisons of the new atypicals for use in psychiatric emergency situations with older drugs (clotiapipe, loxapine) are possible and urgently needed before use of expensive novel atypicals in the emergency situation becomes ubiquitous. Aside from the fact that clotiapipe's possible atypical properties should be studied in more detail, we believe they make this drug most worthy of consideration in further trials on rapid tranquillisation.

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Commentary

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There are scientists who may reason that there is no point addressing a scientific question, someone else has already answered. We know, however, that in real life, science is seldom so cut and dried. Only a very small portion of medical research breaks entirely new ground. Furthermore, an equally small proportion repeats exactly the steps of previous workers. Most research studies will tell us that a particular hypothesis is slightly more or less likely to be correct than it was before they added their new piece to the puzzle. That will be the case only if these research studies were methodologically sound. One of the essential questions, which quite often forms the basis of our decision as to whether a specific research study will influence our practice, is if the study was original.

The practical question to ask, then, about a new piece of research is not “has anyone ever done a similar study before?” but “does this new research add to the literature in any way?” I will come back to this question towards the end of the commentary.

Meta-analysis is defined as a statistical synthesis of the numerical results of several trials which all addressed the same question.¹ It thus increases the effect size of any response difference between agents under consideration. We realize that the whole science of meta-analysis depends on there being several studies in the literature, which have addressed the same question in pretty much the same way. On the face of it the different studies may be quite “unoriginal”.¹

The question asked by Carpenter et al was: “what is the effect of clotiapine for the management of acute psychosis?”

A number of issues are:-

1. Can the scientist compare the management of acute psychosis, even in a heterogeneous condition such as in DSM IV Schizophrenia, nevermind originating from different psychiatric disturbances.
2. What rating-scales were used to measure response in the management of acute psychosis?
3. What is the treatment duration period that will still be classified as the management of acute psychosis?

In the past 10 – 15 years drug trials in psychiatry have become scientific and also easier to compare with each other. Three of

the trials in the meta analysis were conducted in the “good old days” when researchers could modify and use rather unknown rating scales.

The well-known pitfalls when interpreting clinical drug trials surface here:

- lack of power (small sample size)
- possible randomization problems
- ill defined study population
- insufficient report of drop-outs
- inadequate rating scales
- poor control of co-medication
- selective reporting (e.g. what happened to the drop-outs?)
- inadequate statistics

Novartis Pharma state clothiapine to be indicated for the use of a varied number of different psychiatric disorders as well as depersonalization, hyperactivity, sleep disorder and inner uneasiness. This does not sound as if randomized double-blind controlled trials were conducted with an adequate number of patients. Indications like these sound like shotgun therapy. We have surely made scientific progress in psychiatry the last couple of years, with the indications for drug use being more specific.

Coming back to my earlier question as to whether this meta-analysis adds to the literature in any way:

1. We must realize that meta-analysis is not approved as a tool in the regulatory licensing process, for proof of the efficacy of a drug.

2. The suggestion of the authors that Clothiapines’ possible atypical properties should be studied in more detail is debatable given the question as to whether the distinction between atypical and typical antipsychotics is scientifically valid.² I believe that clothiapine should be studied in focussed scientific drug trials, that are well designed, where systematic bias will be avoided and where the study sample is large enough to make the results credible. In my opinion, the meta analysis serves to demonstrate the inadequacies of the existing data.

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