Effectiveness of penfluridol (oral long acting neuroleptic) as compared to second generation oral neuroleptics in psychotic disorder patients: an open label randomized controlled trial.

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Primary Objective: The aim of this study is to determine the time to all-cause discontinuation of penfluridol (acemap; oral long acting neuroleptic) as compared to second-generation oral neuroleptics (olanzapine, risperidone) using an open label...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Schizophrenia and other psychotic disorders
Study type	Interventional

Summary

ID

NL-OMON44089

Source
ToetsingOnline

Brief title
The One for Seven Study: effectiveness of oral antipsychotic agents

Condition

- Schizophrenia and other psychotic disorders

Synonym
Psychotic disorder

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Compliance program, Costeffectiveness, Pharmacological treatment, Psychotic disorders

Outcome measures

Primary outcome

Primary endpoint of the study will be time to all-cause discontinuation,

calculated from the date of randomization to the date of medication

discontinuation according to the discontinuation definition.

Secondary outcome

Secondary endpoints include the reason for treatment discontinuation, and

relationship between efficacy, safety and tolerability, drug attitude,

subjective well-being, insight and compliance, healthcare related costs and

quality of life.

Study description

Background summary

Schizophrenia and its psychotic spectrum disorders are chronic remitting and disruptive disorders associated with significant abnormalities and the progressive deterioration of a wide variety of cognitive, psychosocial, vocational, and behavioural functioning.(Chien and Yip 2013) The fifth edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-V) defines schizophrenia as a syndrome characterized by delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour and negative symptoms, with social dysfunctioning and sometimes mood problems, all for a long duration.(Tandon, Gaebel et al. 2013) Life-time prevalence of schizophrenia is 1%, typically manifesting in late adolescence or early adulthood.(Insel 2010)

With respect to mortality, a substantial gap exists between the health of people with schizophrenia and the general community.(Saha, Chant et al. 2007) Suicide contributes to this increased mortality, however increased mortality risks are also attributable to a wide range of somatic conditions and to reduced access to medical treatment.(Saha, Chant et al. 2007)

To reduce patients* illness episodes and symptoms, as well as to improve their functioning and quality of life in the longer term, comprehensive and multimodal treatment approaches are tested.(Chien and Yip 2013) Antipsychotics are considered the best treatment for schizophrenia and other psychotic disorders.(Miyamoto, Duncan et al. 2005) They are mainly categorized into first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA) and share a similar pharmacological mechanism in blocking the dopamine D2 receptor.(Miyamoto, Duncan et al. 2005)

While pharmacological treatment is the cornerstone and essential component of treatment for schizophrenia and other psychotic disorders(Miyamoto, Duncan et al. 2005), compliance constitutes a major problem in these patients. Most studies indicate that 40-75% of patients stop using their oral neuroleptic during a period of one year.(Lacro, Dunn et al. 2002) (Lieberman, Stroup et al. 2005; Kahn, Fleischhacker et al. 2008) Reasons for non-compliance include lack of insight into the disease, cognitive problems, side effects and negative drug attitude with medication or treatment.(Fleischhacker, Oehl et al. 2003) Non-compliance leads to higher incidence of relapse, hospitalizations, incarcerations, drug and alcohol consumption and suicide.(Acosta, Hernandez et al. 2012)

When second-generation antipsychotics were introduced, this new class of drugs was heralded as the first major advance in the therapeutics of schizophrenia for 40 years.(Lewis and Lieberman 2008) The second-generation drugs appeared to have important advantages over their first-generation predecessors, including better efficacy and improved tolerability.(Lewis and Lieberman 2008) It was also claimed that the higher costs of these drugs would be offset by saving results from decreased use of healthcare services.(Lewis and Lieberman 2008) None the less, the global antipsychotic drug market has increased 30-fold since the late 1980s to more than US 15 billion dollars per year.(Lewis and Lieberman 2008) And meta-analyses and reviews have provided limited support for the superiority of second-generation antipsychotics.(Lewis and Lieberman 2008) (Davis, Chen et al. 2003; Leucht, Wahlbeck et al. 2003) Also large trials did not find this superiority.(Lieberman, Stroup et al. 2005) (Jones, Barnes et al. 2006) As a result, healthcare policy makers on both sides of the Atlantic faced a dilemma with respect to rising costs of mental healthcare and the lack of demonstrably improved outcomes in psychotic disorder patients.(Lewis and Lieberman 2008)

Penfluridol (brand name: acemap) has been available since 1970 as a *unique* neuroleptic used for the treatment of patients with schizophrenia and other

psychotic disorders.(Soares and Lima 2006) It is a typical antipsychotic drug and it is unique in the sense that it can be taken orally once a week; all other oral neuroleptics have to be taken daily, while other long acting neuroleptics need to be injected intramuscularly.(van Praag, Schut et al. 1971; Soares and Lima 2006) Therefore penfluridol is very suitable for patients who have compliance problems, but who refuse intramuscular injections. Penfluridol has a superior effect compared to placebo, and when compared to other typical antipsychotics it shows similar efficacy and tolerance.(Soares and Lima 2006) Compared to depot medication, patients using penfluridol drop out less often, so there is better compliance.(Soares and Lima 2006)

Despite the great advantage of penfluridol regarding compliance, the original pharmaceutical company that produced penfluridol (Janssen Cilag), stopped producing this first-generation antipsychotic in 2009. True reasons for this decision are not known, however it is believed that the production has stopped because the drug lack commercial potential. Janssen Cilag is also a producer of second-generation antipsychotics (risperidone), which has an economic advantage for the manufacturer. Income from oral risperidone are 2.5 times as high as for penfluridol and income from risperidone long acting injections are even 26 times higher as for penfluridol calculated for one year of treatment. Also, in addition to the possible advantage regarding compliance, penfluridol is cheaper than oral second-generation neuroleptics mostly used today (including olanzapine, quetiapine, aripiprazole). Possibly due to these lower financial gains, penfluridol has not been promoted by pharmaceutical companies. From an economical perspective, production of an old antipsychotic that is cheaper than any second-generation antipsychotic is not attractive to other pharmaceutical companies as well. They rather invest in a new medicine with patent that is more profitable.

Considering the clinical importance of penfluridol, the Medicines Evaluation Board (MEB) in The Netherlands has ensured that the production of penfluridol is guaranteed by ordering a pharmaceutical company in the Netherlands. Therefore, penfluridol is still prescribed in the Netherlands in patients with schizophrenia and other psychotic disorders, and is prescribed most frequently in patients who have compliance problems. The use of penfluridol in the Netherlands has increased by 30% in the years 2006 * 2010. The reason for this increase in the use of penfluridol may be that (some) psychiatrists favour penfluridol over other oral neuroleptics, because patients may show better compliance with penfluridol. Penfluridol is also available in other European countries, including Austria, Belgium, France and Germany as well as in some developing countries (Haiti, Philippines) and it is expected that there will be a worldwide interest in this compound because of its low costs and weekly oral dosage scheme.

Because almost all studies on the effectiveness of penfluridol were carried out in the 1970s and 1980s, it is unknown whether penfluridol differs in compliance, efficacy, safety and tolerability, and healthcare costs compared to

second-generation neuroleptics.(Soares and Lima 2006) In case penfluridol leads to increased compliance, we can expect less relapses, higher quality of life, lower number of suicides, less (severe) crisis situations, less incarcerations, and less (in)voluntary hospitalizations. The latter may be the most important financial gain of penfluridol over other oral neuroleptics, since hospitalization costs constitute the largest part of the mental health services budget.(Hoof, Knispel et al. 2012)

This project will provide evidence for the effectiveness of penfluridol as compared to second-generation neuroleptics, which can help in improving compliance and reducing overall costs for the treatment of psychotic disorder patients.

Study objective

Primary Objective: The aim of this study is to determine the time to all-cause discontinuation of penfluridol (acemap; oral long acting neuroleptic) as compared to second-generation oral neuroleptics (olanzapine, risperidone) using an open label randomized controlled trial design in 180 patients.

Secondary Objective(s): Secondary objectives include the reason for treatment discontinuation, efficacy, safety and tolerability, drug attitude, subjective well-being, insight, healthcare related costs and quality of life.

We hypothesize that there will be significant differences in time to discontinuation and overall effectiveness of penfluridol as compared to oral second-generation neuroleptics (olanzapine and risperidone) that reflect variations in compliance, safety and tolerability and costs. We hypothesize that penfluridol as compared to oral second-generation neuroleptics (olanzapine and risperidone), will show better compliance (primary outcome) and therefore lower healthcare costs. Also we hypothesize that higher level of symptom severity, more side effects, poor insight, negative drug attitude and worse subjective well-being would predict poorer adherence associated with more relapses and crises leading to more healthcare use and higher costs.

Study design

Design: Open label, randomized controlled trial in 180 patients
Duration: 4 years
Follow-up: 12 months
Setting: This is a multicenter randomized controlled trial in the Netherlands, supported by the Dutch Psychosis Consortium. Eight mental health institutions collaborate: Academic Medical Center (Amsterdam), Bavo Europoort (Rotterdam), Delta Psychiatric Center (Poortugaal), GGZ Breburg Group (Tilburg),GGZ Noord Holland Noord (Heiloo), GGZ Westelijk Noord Brabant (Halsteren), Maastricht University Medical Center (Maastricht) and Yulius (Rotterdam). Together these

centers treat over 6000 psychotic disorder patients.

The psychiatrists prescribing the neuroleptics as well as the patients cannot be blind to the treatment condition (open label study) due to the different dosing schemes of the neuroleptics (weekly versus daily). But although theoretically this problem may be surmountable, we have chosen to do an open label study because of the important advantages. An open clinical trial with as little exclusion criteria as possible most closely reflects real life clinical practice.(Fleischhacker, Keet et al. 2005) When patients and their treating psychiatrists are unmasked for the assigned treatment, this reflects routine clinical practice, increasing the trial*s external validity; it will also improve the trial*s acceptability for patients and psychiatrists, leading to a group of patients, that is representative of a normal psychiatric case load, which further increased the trial*s external validity.(Kahn, Fleischhacker et al. 2008)
Also, the complicated logistics of a double-blind trial would jeopardize the feasibility of this study, leading to the inclusion of only a selected group of patients. As this selection bias is one of the most serious problems when interpreting and attempting to generalize findings from the available double blind randomized controlled trials(Fleischhacker, Keet et al. 2005), this open randomized design hopefully overcomes this bias problem.

Despite the open label characteristics of the study, we will be able to generate valid results, which do have consequences for clinical practice. All medications used have been shown to have beneficial antipsychotic effects. We have no reasons to believe that clinicians or patients think that one of these substances has more effects on positive symptoms than the others, thereby minimizing the placebo effect. In addition, research data on efficacy, safety and tolerability, drug attitude, subjective well-being, insight, healthcare related costs and quality of life will be collected by trained raters who will be blind for the intervention condition at baseline, at three month and at 12-month follow-up. Demographic characteristics will be registered at baseline including age, sex, country of birth (patient, father and mother), socioeconomic status, level of education, age of onset and duration of untreated psychosis. In addition, psychiatric diagnosis (DSM-V), including comorbid diagnoses such as addiction disorders, of patients will be registered on all five axis by the psychiatrist responsible for the treatment of the patient, as well as date of first contact with mental health services.
At 2, 4, 6, 8, 10, 12 weeks and 6, 9 and 12 months, information about adherence will be collected from the participating centres. Adherence will be measured by pill count in the healthcare setting, where pills remaining in the medication box are counted prior to refill. Besides, the Brief Adherence Rating Scale (BARS)(Byerly, Nakonezny et al. 2008) is used, which will be administered by nurse practitioners who are blinded to electronic monitoring adherence results. They cannot be blinded for the intervention condition since it is necessary to know which medication was used in order to score these variables. This is because penfluridol is taken on a weekly basis, whereas the other drugs are

taken daily. Given these facts, total blinding of this rating is not feasible. Importantly, all raters will be independent, not being clinicians treating the patients or one of the researchers involved. Medication blood level analysis will be used to assess adherence at baseline, three month and twelve month follow-up.

Randomization
Computer generated randomization will be done per site, with help of the randomization program Research Randomizer (www.randomizer.org)(Urbaniak and Plous 2013) following a 2:1:1 procedure into 3 groups: (a) penfluridol group, (b) olanzapine and (c) risperidone group. On the basis of a power analysis (see paragraph 4.4 sample size calculation) 90 patients shall be randomized in group (a) and 90 patients shall be randomized in group (b) or group (c). When patients use olanzapine they cannot be randomized in group (b) and will be randomized in group (a) penfluridol weekly or group (c) risperidone daily. The same applies when patients use risperidone; they cannot be randomized in group (c) and will be randomized to either group (a) penfluridol weekly or (b) olanzapine daily.

Intervention

One group (a) receives penfluridol orally once weekly, group (b) receives olanzapine orally once daily and group (c) receives risperidone orally once daily as prescribed by the treating psychiatrist, according to the prescribing guidelines.
If dosage modifications are needed according to the prescribing psychiatrist, these are allowed within the window of prescribing guidelines.

Study burden and risks

Patients participating in this study, undergo three additional examinations beside their regular check-ups. These consist each of an interview, physical examination and blood sampling. In Appendix 4 of E1. Patient Information leaflet, there is a flowchart with all additional examinations that will take place. At 2, 4, 6, 8, 10, 12 weeks and 6, 9 and 12 months, information about adherence will be collected from the participating centres.

The load of this study is minimal because the additional examinations are scheduled after regular check-ups. The risks of this study are minimal because the study medication used, concerns medication which is also used in regular treatment of patients with a psychotic disorder. Side effects are well known by al the treating psychiatrisct and treatment of this side effects is possible when nessecary.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;1. age 18-65 years
2. psychotic disorder, including schizophrenia, schizoaffective disorder, delusional disorder or psychosis not otherwise specified
3. treatment on an outpatient basis (at the start of the study)
4. psychiatrist treating the patient decides that it is appropriate (based on clinical judgement, guidelines, history and symptoms of the patient) to prescribe either penfluridol, olanzapine or risperidone and that there a no decisive contra-indications
5. patient is willing to use oral neuroleptic treatment, including penfluridol, olanzapine or risperidone
6. able to give informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;1.judicial order stating that taking medication is obliged
2.patient did use penfluridol during the previous six months
3.serious and unstable somatic medical condition
4.insufficient proficiency in Dutch language
5.women who are pregnant
6. patient is on adequate antipsychotic therapy

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	180
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Acemap
Generic name:	penfluridol
Product type:	Medicine
Brand name:	risperdal
Generic name:	risperidon

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	zyprexa
Generic name:	olanzapine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-04-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-003834-21-NL
CCMO	NL51189.078.14