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Masood, Barkat; Lepping, Peter; Romanov, Dimitry; Poole, Robert

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Title: Treatment of alcohol-induced psychotic disorder (alcoholic hallucinosis) - a systematic review.

Authors:

Dr. Barkat Masood, Specialist Trainee 6 General Adult Psychiatry, Betsi Cadwaladr University Health Board (BCUHB), Wrexham, Wales, LL13 7TX. Email: barkat.masood@wales.nhs.uk . Telephone 01978 726873.

Prof. Peter Lepping, Consultant Psychiatrist (BCUHB), Honorary Professor (Centre for Mental Health and Society, Bangor University and Mysore Medical College and Research Institute, India). Email: peter.lepping@wales.nhs.uk

Prof. Dmitry Romanov, Consultant Psychiatrist and Professor of Psychiatry, Department of Psychiatry and Psychosomatics, I.M. Sechenov First Moscow State Medical University, Moscow, Russia; and Mental Health Research Center, Moscow, Russia). Email: dm.v.romanov@mail.ru

Prof. Rob Poole, Consultant Psychiatrist (BCUHB) and Professor of Social Psychiatry (Centre for Mental Health and Society), University of Bangor, Bangor, Wales. Email: rob.poole@wales.nhs.uk

Short Summary: This systematic review of alcohol-induced psychotic disorder treatment found 15 studies and 10 case reports of relevance. Older studies of first-generation antipsychotics reported full or partial remission in most patients, as did newer studies with second-generation antipsychotics. Novel drugs reported low remission rates. Standard alcohol withdrawal treatments were successful.

MeSH terms / Key words: Psychoses, Alcoholic; Treatment; Treatment outcomes; Hallucinations, Verbal Auditory; Hallucinations, Organic; Review, systematic; Drug therapy; Alcoholism.

Running Head: Review of alcoholic hallucinosis treatment.

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Declarations of Interest

All authors have no declarations of interest.

Treatment of alcohol-induced psychotic disorder (alcoholic hallucinosis) - a systematic review.

Barkat Masood, Peter Lepping, Dmitry Romanov, Rob Poole.

Abstract

Background

Alcohol-induced psychotic disorder (AIPD) is described by ICD-10 and DSM-5. It is a condition that is distinct from schizophrenia and has a close relationship with alcohol withdrawal states. There is sparse evidence to guide treatment of AIPD.

Aims

To evaluate the effectiveness of evidence based treatments for AIPD.

Method

A systematic review using PRISMA guidelines was conducted.

Results

Of 6,205 abstracts found, fifteen studies and ten case reports met criteria and were examined. Larger studies examined the use of first generation antipsychotic drugs, reporting full or partial remission in most patients. Newer case reports report similar results using second generation antipsychotic drugs. Novel treatments, such as those acting on GABA receptors reported low numbers of patients in remission. Some large studies report the successful use of standard alcohol withdrawal treatments.

Conclusion

The findings of our systematic review are inconclusive. There was significant heterogeneity between and within studies. Significant publication bias is likely.

Randomised control trials of more carefully delineated samples would produce evidence of greater clinical utility, for example on differential effectiveness of antipsychotics and optimal length of standard alcohol withdrawal treatments. AIPD patients who show poor treatment responses should be studied in greater depth.

Background

Excess alcohol consumption results in medical and social problems around the world. It accounts for 3% of global deaths (Rehm *et al*, 2009). Neuropsychiatric consequences to alcohol dependence syndrome include delirium tremens, alcohol-related brain damage, Korsakoff's syndrome and alcoholic hallucinosis. The terms "alcoholic hallucinosis" and "alcohol-induced psychotic" disorder (AIPD) are often used interchangeably, although they may be better regarded as over-lapping categories. In this review we follow ICD-10 (WHO, 1992) in using the rubric AIPD to include both syndromes (ICD-10 code F10.5, corresponding to DSM-5 code 292.1).

According to ICD-10 (WHO 2016 version), AIPD is a condition where mental and behavioural symptoms manifest within 2 weeks of alcohol use and must persist for more than 48 hours. Symptoms should not arise as part of alcohol intoxication or an alcohol withdrawal state. Clouding of consciousness should not be present to more than to a minor degree. An episode can persist for up to six months. A wide variety of symptoms can occur, including schizophreniform delusions, hallucinations, depression and mania. DSM-5 (APA, 2013) specifies that the substance should be capable of causing symptoms and that the condition should not be better explained by another psychotic disorder.

There are a number of assertions made within the AIPD literature. In a Finnish study, AIPD was found to have a general population lifetime prevalence of 0.41%, or 4% for people with alcohol dependence syndrome. It was most common amongst men of working age (Perälä *et al*, 2010). AIPD is said to manifest immediately after the consumption of large amounts of alcohol. It may not be related to duration of alcohol

dependence syndrome (George & Chin, 1998; Perälä *et al*, 2010). Symptoms may develop during alcohol intoxication or withdrawal or soon thereafter. The diagnosis cannot be made until clear consciousness is restored. AIPD is said to usually resolve within 18 to 35 days with antipsychotic and/or benzodiazepine treatment (Vicente Muelas *et al*, 1990). A minority of patients may have persistent symptoms for six months or more (Benedetti, 1952; Bradley-Burton, 1958). AIPD may end through alcohol abstinence alone and return soon after reinstatement of drinking (Glass, 1989b). The assertion that antipsychotic drugs are the treatment of choice (Jordaan & Emsley, 2014; Soyka, 1988) is not supported by published randomised controlled trials (RCTs). A number of factors affecting people with AIPD make it difficult to recruit and retain participants in RCTs (Perälä *et al*, 2010).

There are few rigorous published studies of treatments for AIPD. This systematic review was conducted in order to evaluate the available evidence on treatment.

Methods

PRISMA Guidelines were used to carry out a systematic review. Medline, EMBASE, PsychINFO, Cochrane and CINAHL databases were searched for studies that had been published between 1st January 1900 and 18th August 2016. Subject search terms were: hallucinations / or alcoholism / or psychoses / or alcoholic psychoses / or chemically induced, drug therapy, prevention & control, rehabilitation, therapy / or alcohol intoxication / or delusions / or delirium / or dissociative disorders. (Search strategy available on request.)

Initial inclusion criteria for screening purposes were articles that:

- had been published in any language,
- investigated alcohol with or without polysubstance misuse,
- investigated hallucinations,
- investigated hallucinations attributed to alcohol and polysubstance misuse,
- investigated hallucinations that persisted beyond one week of alcohol/drug withdrawal state,
- investigated any treatment of symptoms,
- investigated any outcome measures,
- investigated patients of any age,
- were RCTs,
- were case reports or series.

There were eight exclusion criteria during the screening phase:

- papers that did not have abstracts (Criterion 1),
- non-human studies (Criterion 2),
- examined acute confusional states/delirium, symptoms that occurred during alcohol/drug withdrawal states of less than one week duration, delirium tremens, drug intoxication states and organic psychoses (Criterion 3),
- did not examine hallucinations or psychoses (Criterion 4),
- examined schizophrenia, bipolar disorder, mood disorder or delusional disorder (Criterion 5),
- did not examine alcohol related hallucinosis or examined hallucinations due to polysubstance misuse (Criterion 6),
- single case studies (Criterion 7) and
- did not examine treatment or include outcome measures (Criterion 8).

The minimum standard for outcome measures was classification into no remission, partial remission or full remission.

RESULTS

7,347 articles were identified and 6,205 remained after duplicates were removed.

Abstracts for the 6,205 articles were screened and the 8 exclusion criteria applied.

Twenty-six full text articles were requested to assess eligibility. (See PRISMA flow chart Figure 1.)

In December 2016, a search on the ClinicalTrials.gov (www.clinicaltrials.gov), the ISRCTN Registry (www.ISRCTN.com), the EU Clinical Trials (www.clinicaltrialsregister.eu) and the UK Clinical Trials Gateway (www.ukctg.nihr.ac.uk) websites did not find any completed or ongoing RCTs of treatment of AIPD.

Fifteen studies (for details see Table 1) and ten case reports (Table 2) on the treatment of AIPD were included in the final analysis. A meta-analysis with funnel plot was not conducted because studies were few and too heterogeneous.

Trial studies: Four studies retrieved were double blind RCTs, of which one was a crossover study. One study included comparison with a group of participants with a diagnosis of paranoid schizophrenia. Ten studies were open label, non-comparative case series of treatment and outcome of AIPD.

Five of the included studies examined cases of AIPD arising in the context of alcohol withdrawal (psychotic symptoms started during the withdrawal state but persisted after other withdrawal symptoms had resolved). The trials are summarised in Table 1.

Table 1 about here

Types of treatment

1. Antipsychotics: No trials examined the use of second-generation antipsychotics. Six trials examined the use of single or multiple first generation antipsychotics, including haloperidol, chlorpromazine, trifluoperazine, reserpine, thiotixene and levopromazine.

Three trials examined the use of antipsychotics, benzodiazepines, vitamin B1 with treatment outcomes, but did not specify which antipsychotic drug was used.

2. Anticonvulsants: Anticonvulsants were used in three trials (lamotrigine, sodium valproate and phenobarbitone). Hypnotics such as barbamyil and chloral hydrate were used in one trial.

3. Others: Two trials examined other compounds that act on GABA receptors (piracetam and clorazepate).

One trial examined the primary use of an unusual treatment (glycine). One trial examined the use of electroconvulsive therapy (ECT)

Treatment results:

There was marked heterogeneity of results, even with the same drug. For example, full remission rates for chlorpromazine varied from 0% to 68%, and partial remission rates from 0% to 32%. Better results with haloperidol included full remission rates of 68% to 90%, and partial remission rates of 0% to 30%. However, there were few trials of antipsychotic monotherapy, so findings are hard to fully interpret.

Heterogeneous outcomes were also evident in trials of non-antipsychotic treatments, apart from one trial of three patients treated with ECT, all of whom experienced full remission.

Treatment duration ranged from 3 days to 546 days, but most trials were brief.

Longer duration was not associated with more favourable outcomes. In three trials, duration was not stated.

Participants were predominantly male, as noted by Szeffal & Zaleski (1983), who studied women with AIPD. Cohort sizes ranged from 3 to 100. Ten trials involved between 24 and 40 participants.

Case reports

The ten case report papers reported 13 separate patients who were exposed to 21 different treatments or treatment combinations. All patients were treated with first- or second-generation antipsychotics. Three patients were treated with adjunctive benzodiazepines and vitamin B1.

Table 2 about here

Treatments and outcomes are set out in Table 2. Outcomes were highly variable. Five patients experienced full remission with risperidone and two with olanzapine. No remission occurred in patients treated with chlorpromazine, perazine, flupenthixol, trifluoperazine or quetiapine. Of three treatment episodes with haloperidol, only one led to (partial) remission. There were two electroconvulsive therapy treatment episodes, both of which were associated with full remission. However, it should be noted that the most recent report of ECT for AIPD was published in 1956.

Full remission was reported in one patient treated with transcranial direct current stimulation following failure of three different first generation or second generation antipsychotic drugs

Discussion

Previous reviews of AIPD have focussed on aetiology, symptoms, prognosis and the relationship with schizophrenia (Soyka, 1994; Jordaan & Emsley, 2013; Engelhard *et al*, 2015). This is the first systematic review to examine treatment of AIPD. We included part of the non-English language literature, papers written in Dutch, French, German, Polish, Russian and Spanish. All papers were translated by PL or DR who are fully fluent in the respective languages, with the exception of Polish and Spanish where Google translate was used.

Main Findings

The findings of our systematic review are inconclusive. Studies generally had relatively low numbers of participants. There were few RCTs. Treatments were sometimes idiosyncratic, although these were usually supported by a rationale. For example, Aliyev and colleagues (Aliyev & Aliyev 2005,2008; Aliyev *et al*, 2011) justified their treatment with glycine, lamotrigine and sodium valproate by reference to Branchey *et al* (1985), who suggest that amino acid abnormalities affect cerebral serotonin and dopamine levels and thus cause hallucinations. Their results do not support the use of these treatments. They reported high partial remission rates in RCTs but the trials were brief (10 days) with no indication of longer-term outcomes. High doses of medication were used. These may have caused sedative side effects, confounding findings of partial remission.

Overall, larger studies tended to report at least partial remission on antipsychotic medications, whether in combination with other treatments or as monotherapy. Some case reports concerned treatment with second-generation antipsychotics. Insofar as it is possible to tell, these appear to be no better or worse than older drugs.

Problems in studying treatments for AIPD

The sparseness of the literature is surprising, as alcohol dependence syndrome is common and AIPD is a serious complication of the condition. However, there are several problems in studying treatments for AIPD:

Firstly, it may be difficult to recruit and retain participants who are both alcohol dependent and suffering from psychotic symptoms. Prolonged abstinence can be

difficult to achieve. Participants are likely to live in difficult social situations due to alcohol excess (Ali & McBride, 1997). These factors make compliance and retention in rigorous trials difficult.

Secondly, poor treatment outcomes in longer studies may lead to participants dropping out of trials. Under-powered trials generate inconclusive results.

Heterogeneous samples

The literature on AIPD and alcoholic hallucinosis has been dominated by attempts to ascertain whether there is a single syndrome, distinct from schizophrenia and delirium tremens, or whether there are several alcohol-related psychotic syndromes, either discrete or overlapping.

We found that all studies and case reports matched ICD-10 and DSM-5 criteria. All studies and case reports excluded clouding of consciousness as a key diagnostic criterion, which is congruous with DSM-5 and ICD-10 criteria. All case reports and studies described auditory hallucinations as a key feature in AIPD but some authors reported hallucinations in other modalities. Auditory hallucinations were second and third person, commentary, derogatory and command types. Delusions of persecution and of jealousy were reported in some participants. Boriskov (1977) described delusions of grandeur in AIPD, while Jordaan *et al* (2012) found no evidence of significant delusions of grandeur. Interestingly, a few studies reported schizophreniform thought disorder (George & Chin, 1998; Vicent-Muelas *et al*, 1990). All authors reported that the onset of auditory hallucinations could occur

during excess alcohol consumption or on alcohol withdrawal. No auditory hallucinations commenced during periods of extended alcohol abstinence.

The diagnosis of AIPD appears to have been stable in all studies. No changes of diagnosis to schizophrenia were observed. However, some participants experienced alcohol withdrawal symptoms, there was a wide range of psychopathology in different participants, and the timing of onset of AIPD was not always reported.

Attempts have been made to distinguish between AIPD and schizophrenia complicated (or precipitated) by alcohol misuse. In the 1950s, three large-scale studies followed patients with AIPD for 5 to 23 years in order to examine prognosis and diagnosis (Benedetti, 1952; Burton-Bradley, 1958; Victor & Hope, 1958). The conclusion was broadly similar: the majority of patients studied did not have schizophrenia. Cutting (1978) concluded from a study of 46 patients that AIPD could be regarded as an organic psychosis, and if there was any resemblance to schizophrenia this was due to an emphasis on Schneider's first rank symptoms in earlier editions of ICD and DSM. He suggested that people with AIPD do not show features of schizophrenia as propounded by Bleuler (1911) -such as blunting of affect, autism, thought disorder and ambivalence - and by Kraepelin (1913).

A two part review by Glass (1989) emphasised that schizophrenia and AIPD have different onsets, different symptoms and different outcomes. This view was shared by Soyka (1994), who had reported that patients with AIPD were more likely to have a family history of alcohol misuse than psychosis, and vice versa for patients with schizophrenia (Soyka, 1990). A number of family studies support a genetic distinction

between AIPD and schizophrenia (Schukit & Winokur, 1971; Rimmer & Jacobsen, 1977; Kendler, 1985).

Case reports

These did not add significantly to our understanding of treatment strategies for AIPD. We found only ten case reports (See Table 2). Treatment periods were usually around 56 days duration (Chaudhary & Augustine, 1991; Soyka, 1997; De Millas & Haasen, 2007; Bouritius *et al*, 2015; Goyal, 2016). Full or partial remissions occurred within a matter of days or not at all.

Remission on treatment with first generation antipsychotics was common, but some reported success with subsequent use of second-generation antipsychotics, strengthening the suspicion of publication bias. Only one case report reported no treatment remission (Hytinnen, 1987). Case studies are well recognised to be potentially misleading, and we do not believe that any reliance should be placed upon them.

Non-pharmacological treatment strategies

In a very small number of cases, ECT and transcranial direct current stimulation appeared to be effective treatments (Gruenberg, 1940; Bourdon, 1952; Goyal, 2016). These findings are interesting but require replication in large studies.

There is a widely held clinical dictum that alcoholic hallucinosis does not resolve without complete abstinence from alcohol and that relapse of drinking tends to cause a return of hallucinations soon thereafter. Abstinence on its own was not an effective treatment for AIPD in one case report (De Millas & Haasen, 2007). Nonetheless, this is a safe treatment strategy, and it is surprising that there are no studies reported anywhere in the literature of alcohol withdrawal followed by complete abstinence with no drug treatment. This is a major gap in the evidence base.

Recommendations for future research

There is a prima facie case that the rubric AIPD is too broad to allow clear findings for treatment of different sub-types to be evident. This is evident in both DSM-5 and ICD-10 criteria. There is no evidence base to fall back on underpinning a pragmatic sub-classification. Although it is reasonable to conduct rigorous trials of treatment for a broad range of psychotic symptoms, we suggest that it would be helpful if future trials attempted to identify participants with relatively homogenous symptoms. The key variables to take into account are:

1. Did psychotic symptoms first arise during alcohol intoxication or, conversely, during acute alcohol withdrawal?
2. Are symptoms predominately hallucinations, delusions, or both?
3. Is symptom duration one month, more than one month or more than six months?
4. Do symptoms persist during abstinence?
5. Is schizophreniform thought disorder present?

Greater clarity and homogeneity would distinguish, for example, participants who meet criteria for both schizophreniform psychosis and alcohol dependence syndrome from participants displaying a core “alcohol hallucinosis” as described by Lishman (1998), with persistent vivid auditory hallucinations that arise with a quality of insight, but few or no other psychotic symptoms.

Clinical implications

Our systematic review suggests that there is adequate evidence that some patients with AIPD show a favourable response to antipsychotic medication. There is nothing to indicate the superiority of any particular drug. Both first- and second-generation drugs appear to be effective. However, it seems highly likely that many patients show little or no response to antipsychotics and that persistence when they fail to produce remission (whether partial or full) cannot be justified. There is no evidence to guide the duration of treatment. First principles would dictate that this should be as brief as possible, given the wide range of side effects associated with these medications.

As complete abstinence from alcohol, when it can be achieved, slows or stops other alcohol-related disease processes, there is good reason to strongly recommend it. There is sufficient weight of clinical opinion to caution patients that even controlled drinking may lead to the return of psychotic symptoms.

There is insufficient evidence for other treatments reviewed here to recommend their routine use in the treatment of AIPD

Conclusion and limitations:

Given the relative dearth of data we chose a wide timeframe for our search. However, earlier papers may have included patients who may have been excluded if modern diagnostic techniques had been available. Furthermore, standard treatments such as antipsychotics were not available for a proportion of the early studies. Much of the evidence for treatment of AIPD is weak and is only level IV evidence (Agency for Health Care Policy and Research, 1992). The lack of research on AIPD may be due to a belief that it is easy to treat (Jordaan & Emsley, 2014; Soyka, 1988). However, this is mistaken as hospital readmission rates are high (Soyka *et al*, 2013). There is little clarity on how best to treat patients with persistent symptoms.

Heterogeneity is a problem in the studies found. We suggest that distinguishing between key variables of AIPD would help to understand the findings of future treatment trials.

The evidence for the effectiveness of first- and second-generation antipsychotic drugs is based upon case reports and underpowered trials. Positive publication bias is likely. A funnel plot was not feasible due to the size and nature of the literature. There is supportive evidence to use this treatment, but better evidence is needed. Similar considerations affect studies using novel treatments such as GABA receptor compounds, but the lack of positive findings means that they cannot be recommended in the treatment of AIPD. Although some larger studies report the successful use of standard alcohol withdrawal treatments, longer term management remains

unexamined. There is an important gap in the literature on the management of patients whose symptoms fail to remit in response to antipsychotic medication.

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Author	Study Type	Treatment and Outcome measurement	Duration (days)	N, age range	Outcome: no remission, partial remission and full remission.
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Gruenberg (1940)	Case series*	Electroconvulsive therapy wavelength 7.5 metres; 15 minutes per treatment. Self structured scale of improvement or no improvement.	5, 6 & 14 treatments. Maximum 28 days. *	Males 3; aged 28 -40.	Full remission: 3 (100%) *
Bobrov (1966)	Case series (Observational study)	Chlorpromazine, antidepressants, psychotherapy.	Unknown	100 patients	No remission: 100 (100%)
Morales- Beda & de Haro de La Cruz (1968)	Case series	Neuroleptic free prior to treatment. Thiotixene 30 - 60mg /day.	56-252	Males 6	No remission: 6 (100%)
Entin (1970)	Case series**	Vitamin B1. Reserpine 6-20mg/day. Haloperidol 5-10mg/day. [Chlorpromazine, Levopromazine and Trifluoperazine. Barbamyl, phenobarbitone, barbital sodium, chloral hydrate also used .Doses unknown].	28-168	73 patients	Full remission: 50 (68%) Partial remission: 23 (32%)**
Boriskov (1977)	Case series (Open label. observational study)	Antipsychotics, vitamin B1 (100- 200mg) and Biyohinol/ Bioochinolum preparation (quinine bismuth iodide) up to 40- 50ml	28	46 patients	No remission: 46 (100%)

Sampath et al (1980)	Case series (Prospective observational comparison study)	Initial period -chlorpromazine or Trifluoperazine (dose equivalents chlorpromazine 400mg- 1200mg). Then Chlorpromazine or trifluoperazine (dose equivalents chlorpromazine 300-1,000mg). Self constructed outcome scale of full remission, partial remission and no remission.	Initial period-42 days. Then 546 days.	30 patients with alcoholic hallucinosis (ICD-9 criteria) compared with 30 patients with paranoid schizophrenia.	Alcoholic hallucinosis: Full remission: 19 (63%), Partial remission: 7 (23%), No remission: 4(13%). Paranoid schizophrenia: Full remission: 4(13%), Partial remission: 11 (37%), No remission: 15 (50%).
Kabas (1985)***	Double blind randomised placebo controlled .Cross over trial***	Piracetam 9.0g/day and IV Diazepam up to 20mg/day. Brief Psychiatric Rating Scale.	6	24 male patients (16 withdrawal states and 8 alcohol hallucinosis)	Total patients: partial response: 21(100%). 21 completed, 3 in first placebo period withdrawn due neuroleptic use. 1 patient of initial piracetam group required IV diazepam. 7 of placebo required IV diazepam. Alcohol hallucinosis: partial remission: 8 (100%)***
Vencovsky et al (1985)	Case series†	Clorazepate 200mg - 600mg/day (Intra muscularly or intravenously). Oral clorazepate used after parenteral treatment. Brief Psychiatric Rating Scale	2-3	35 patients (21 delirium tremens and 14 alcoholic hallucinosis).	Alcoholic hallucinosis: Full remission: 8 (57%). No remission: 6(43%) following parenteral treatment.†
Vicente-Muelas , Rios Rial & Ochoa Mandago	Case series	Antipsychotics, benzodiazepines and vitamin B1 (No names or doses). Self constructed scale: full remission, partial remission, no	18 - 35	25 (23 male and 2 female)	Full remission: 16 (64%), Partial remission: 6 (24%), No remission: 3 (12%).

(1990)		remission.			
George & Chin (1998)	Case series††	Diazepam 30-40mg/day. Vitamin B1 (1 ampoule/day) for 3 days, then 200mg/ day. Haloperidol 30-40mg/day. Self constructed scale of full recovery or no recovery.	Mean duration: 7 days	34 patients (32 male and 2 female)	Full remission: 27 (85%), No remission: 5 (15%).†† 32 eligible patients as 2 had delirium tremens, 1 of these died.
Aliyev & Aliyev (2005)	Double blind randomised placebo controlled trial.	700mg sublingual glycine /day. 5 point scale (1=absent, 2=slight, 3=moderate, 4=significant, 5=high), Wilcoxon Rank Sum test.	7	40 male patients. 20 to drug and 20 to placebo.	Sublingual glycine: partial remission: 20 (100%) Placebo: no remission: 20 (100%)
Aliyev & Aliyev (2008)	Double blind randomised placebo controlled trial.	Sodium Valproate. Starting dose of 1,000mg/day, increased to 3,000mg. Clinical Global Impression improvement scale.	Initial dose titration 3. Total period- 10.	40 male patients.	Sodium valproate (19 completers): Partial remission: 14 (74%), No remission: 5 (26%). Placebo (20 completers): Partial remission: 5 (25%), No remission: 15 (75%).
Aliyev et al (2011)	Double blind, randomised placebo controlled trial.	Lamotrigine 300mg/day. Positive And Negative Symptoms Scale, subscale for hallucinosis.	10	40 patients. 20 lamotrigine, 20 placebo.	Lamotrigine: partial remission: 20 (100%) Placebo: no remission: 20 (100%)
Aleksin & Egorov (2011)	Case series(Observational study)†††	Antipsychotics, benzodiazepines and vitamin B1.	Unknown.	26 males ##	Full remission: 24 (92%), Partial remission: 2(8%). †††

Jordaan et al (2012)	Case series. (Prospective open label non comparative study)	Haloperidol 5 mg /day. Extra pyramidal side effects treated with benhexol (2-6mg/day) and lorazepam (max 4mg/day) for sedation/anxiety, infrequently used. Positive and Negative Symptoms Scale.	42	20 patients (16 male and 4 female)	Full remission: 18 (90%), partial remission: 2 (20%).
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Table1. Treatments and Outcomes in AIPD studies.

*Assuming maximum of 2 treatments per 7 days. Although 2 or more treatments could occur in a day.

** Unknown regimen. Original sample n=204. Mixture of delirium tremens, organic brain syndromes and AIPD. Relevant AIPD cases examined.

*** Assuming that 3 participants withdrawn due to severity of withdrawal state and subsequently requiring antipsychotics.

† 29 patients had full remission. It is assumed that all 21 patients with delirium tremens had full remission.

†† 28 of 33 patients had complete remission. However, the adjustment of removing 1 patient is because this patient had delirium tremens and is assumed to have had full remission.

††† Original mixed study (clearly defined cases of delirium tremens, AIPD, Korsakov's syndrome and other psychiatric disorder due to alcohol and psychostimulants) of n=125.

Table2. Treatment and outcomes in AIPD case reports.

Authors	N	Age (years)	Sex	Treatment	Dosage per day. (mg)	Duration(days)	Outcome
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Bourdon (1956)	2	50	M	Chlorpromazine	Unknown	Unknown.	No remission,
				Electroconvulsive treatment.		1 session.	Full remission.
	55	M	Electroconvulsive therapy.	Unknown	1 session.	Full remission.	
Hytinnen (1987)	1	35	M	Haloperidol	Unknown	6	No remission
Chaudhary & Augustine (1991)*	2	40	M	Antipsychotics, vitamins,psychotherapy, supportive measures	Unknown	56	Full remission*
					Unknown	168	Full remission*
Soyka (1997)**	1	33	M	Haloperidol decanoate	10	2190	No remission**
				Perazine	200		
				Risperidone	6	56	Full remission**
De Millas & Haasen (2007)	1	58	M	Risperidone. Alcohol abstinence.	2	5	Full remission.
					4	56	Full remission.
Kumar & Bankole*** (2010)	1	40	M	Olanzapine	20	10	Full remission***
				Citalopram.	40		
				Risperidone.	6	10	Full remission***
Farcas (2012, 2016)†	2	23	M	Risperidone, benzodiazepines and vitamin B1.	4	42	Full remission†
					4	42	Full remission†
Ogut, Suner & Citak	1	58	M	Diazepam	60	Unknown	Full remission
				Olanzapine	10		

(2014)				Folic Acid and Vitamin B complex.	Unknown	Unknown	
Bouritius, Neven & Blom (2015) ^{††}	1	38	M	Quetiapine,	900	56	No remission ^{††}
				Flupenthixol	18	56	No remission ^{††}
				Haloperidol	Unknown	Unknown	Partial remission ^{††}
Goyal (2016) ^{†††}	1	59	M	Trifluoperazine	10	56	No remission ^{†††}
				Risperidone	6	56	No remission ^{†††}
				Clozapine.	200	56	No remission ^{†††}
				Transcranial direct current stimulation(tDCS)	2 sessions per day, 2mA intensity.	5	Full remission ^{†††}

Please note: Outcomes dictate that an individual treatment episode occurred. Some patients received more than one treatment. Whenever more than one treatment is listed for a patient, the treatments listed were given consecutively.

*Full remission after 56 and 168 days. Time of response suggested to be immediate.

** Full remission occurred after a few days.

*** Dose of risperidone not specified. Assumed to be maximum doses, as per British National Formulary 70 (2015).

†Four milligrams refers to dose of risperidone. Unknown type, dose and duration of benzodiazepine. Confirmed by email correspondence from B Masood to A Farcas.

†† Doses and duration not specified for quetiapine and flupenthixol. Assumed to be adequate therapeutic trial at maximum doses, as per British National Formulary 70 (2015).

†††Auditory Hallucinations Rating Scale used.

Figure 1: PRISMA flow diagram of treatment of AIPD.



