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McKetin, Rebecca; Dean, Olivia M.; Baker, Amanda L.; Carter, Greg; Turner, Alyn; Kelly, Peter J.; Berk, Michael; "A potential role for N-acetylcysteine in the management of methamphetamine dependence". Published in *Drug and Alcohol Review* Vol. 36, Issue 2, p. 153-159 (2017)

Available from: <http://dx.doi.org/10.1111/dar.12414>

This is the peer reviewed version of the following article: McKetin, Rebecca; Dean, Olivia M.; Baker, Amanda L.; Carter, Greg; Turner, Alyn; Kelly, Peter J.; Berk, Michael; (2017), "A potential role for N-acetylcysteine in the management of methamphetamine dependence", *Drug and Alcohol Review*, which has been published in final form at <http://dx.doi.org/10.1111/dar.12414>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Accessed from: <http://hdl.handle.net/1959.13/1333204>

A potential role for N-acetylcysteine in the management of methamphetamine dependence.

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Running head: N-acetylcysteine for methamphetamine

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Word count =2,477 16 pages, 1 table

Refs = 57

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Abstract

Methamphetamine dependence is a growing problem in Australia and globally. Currently there are no approved pharmacotherapy options for management of methamphetamine dependence. N-acetylcysteine (NAC) is one potential pharmacotherapy option. It has received growing attention as a therapy for managing addictions because of its capacity to restore homeostasis to brain glutamate systems disrupted in addiction, and thereby reduce craving and the risk of relapse. NAC also has anti-oxidant properties that protect against methamphetamine-induced toxicity and may therefore assist in the management of the neuropsychiatric and neurocognitive effects of methamphetamine. This commentary overviews the actions of NAC and evidence for its efficacy in treating addiction with a particular focus on its potential utility for methamphetamine dependence. We conclude that the preliminary evidence indicates a need for full-scale trials to definitively establish whether NAC has a therapeutic benefit, and the nature of this benefit, for managing methamphetamine dependence.

Keywords: Methamphetamine, treatment, pharmacotherapy, drug therapy, N-acetylcysteine

Methamphetamine ('ice' or 'crystal meth') is a significant and growing public health concern in Australia [1], a situation that mirrors global trends [2], with the number of estimated dependent users having risen to 160,000 in 2013/14 (1.2% of Australians aged 15 to 54 years), up from 58,000 in 2009-2010 [3]. This has substantially increased the number of methamphetamine-related presentations to drug treatment services, hospitals and emergency medical facilities in Australia [4], while broader community concern, particularly about increasing use among young people in rural communities and remote areas, has led to a spate of community forums [5], government-led inquiries [6] and a National Ice Taskforce [7].

Despite its gravity as a public health issue, the evidence base for treating methamphetamine dependence is extremely weak with few adequately-powered randomised controlled trials [8,9]. Psychological therapies can produce small to moderate reductions in methamphetamine use when delivered intensively in clinical trials [10], but they have been poorly translated into clinical practice [11]. Community-based treatment options, such as residential rehabilitation, can produce good short-term benefits, but they tend to be very costly and relapse rates are incredibly high [12]. Poor outcomes for psychosocial treatments have been related to cognitive impairment [13], possibly related to methamphetamine neurotoxicity [14].

Clinicians are also challenged by the high rates of psychiatric symptoms in this population, including agitation, mood swings and paranoia during the initial weeks of detoxification.

To-date there are no approved pharmacotherapies for methamphetamine dependence (akin to opioid substitution therapy for heroin dependence) [8]. This is partly because of insufficient research evidence to identify safe and effective options, but also a failure to find preliminary signs of efficacy for therapies that have been trialed. Most of these pharmacotherapy trials have focussed on agonist therapies that substitute methamphetamine with similarly acting drugs, essentially mimicking the actions of methamphetamine to normalise brain function and

reduce drug craving. This approach includes the off-label use of dexamphetamine (up to 80 mg oral daily doses) as a treatment for stimulant dependence [15]. Although intuitively appealing, and despite the success of agonist therapy for opioid dependence (i.e. methadone and buprenorphine [16]), dexamphetamine, and most similar acting agonist therapies, have failed to significantly reduce methamphetamine use, over placebo, in controlled clinical trials [8].

Glutamate function as a new therapeutic target in addiction

Recent developments in our understanding of the neurobiological underpinnings of addiction suggest that targeting alterations in glutamate function may prove promising [17]. One of the maladaptive processes at play in addiction is astrocyte dysfunction in the region of the nucleus accumbens, which causes aberrant potentiation of glutamate transmission in the projections from the prefrontal cortex to the nucleus accumbens [17]. Of particular importance in this process is the glial glutamate transporter 1 (GLT1) which is located near the synaptic cleft. This functions to minimise spill over of glutamate into the non-synaptic extracellular space. Nucleus accumbens GLT1 receptors are down-regulated following long-term exposure to addictive drugs. This decreases the elimination of synaptic glutamate, and thereby increases spill over into the post-synaptic space, activating extracellular glutamate receptors and calcium mediated excitotoxic processes, risking apoptosis and ferroptosis [18].

In addition, excess glutamate levels are further exacerbated by the reduced capacity of presynaptic glutamate auto receptors (mGluR2) to inhibit glutamate release into the post-synaptic cleft. Extra-synaptic spill over of glutamate also strengthens glutamatergic synapses in the accumbal region [19]. This synaptic potentiation of glutamate is thought to cause an abnormally elevated glutamate response to drug intake and additionally appears to be central to drug-seeking and relapse [19].

Conversely, withdrawal from exposure to stimulant drugs (methamphetamine, cocaine and nicotine) produces a reduction in basal levels of extra-synaptic glutamate in the nucleus accumbens [17,20]. Most extracellular glutamate is supplied by local glial cells via the cystine-glutamate exchanger, which exchanges extracellular cystine for intracellular glutamate [17]. Chronic exposure to some drugs (e.g. cocaine and nicotine), but not others (heroin), has been shown to reduce the expression of the catalytic subunit of the cystine-glutamate exchanger (xCT), presenting a potential mechanism through which chronic drug exposure may alter synaptic potentiation within the accumbal region [17]. Although methamphetamine might upregulate transcription of xCT, this is yet to be established, and the relative contributions of this system and GLT1 in methamphetamine addiction and their interactions remain to be fully elucidated [21,22].

Boosting cystine levels by administration of cysteine, or its prodrug, N-acetylcysteine (NAC), has been found to restore extracellular glutamate levels in animals withdrawn from chronic cocaine administration [23]. This cystine-mediated increase in basal extracellular glutamate prevents the excessive levels of glutamate seen following a challenge dose of the drug, as described above, which in turn blocks the reinstatement of drug seeking normally seen in chronically drug-exposed animals [23]. This additionally reduces methamphetamine-related oxidative stress and blocks apoptosis and ferroptosis cell death pathways [24]. NAC facilitation of the cystine-glutamate exchange in the nucleus accumbens, and its consequent effects, are contingent on prior exposure to the addictive drug, with no direct effects seen on drug administration per se, or on other rewarding behaviours (e.g. food intake) [23]. These effects have to-date been observed specifically for cocaine and are yet to be confirmed for methamphetamine and other drugs.

N-acetylcysteine (NAC) as a potential modulator of glutamate function

The discovery that the cystine-glutamate exchange plays an important role in drug seeking and relapse has led to a search for pharmacotherapies that can restore glutamate homeostasis in addiction. NAC is a promising candidate because of its capacity, as a cysteine prodrug, to restore homeostasis to glutamate function in drug-exposed animals, and inhibit drug-primed relapse, as described above. NAC is a common dietary supplement that serves as a pro-antioxidant to glutathione and is used to treat paracetamol overdose. The actions of NAC are multi-faceted and include antioxidant activity, reduction of inflammatory cytokine release, modulation of dopamine release, reversal of models of mitochondrial dysfunction, reductions in apoptosis and ferroptosis, increased neurogenesis as well as increased glial-glutamate release through the activation of the cystine-glutamate antiporter, xCT [17].

Potential benefits of NAC for specific methamphetamine-related psychopathology

Aside from its ability to restore glutamate homeostasis in addiction, the antioxidant properties of NAC can protect against methamphetamine-induced neurotoxicity [25]. Specifically, neurotoxicity can result from the oxidative stress that occurs when normal metabolic processes are unable to cope with the large efflux of dopamine that occur following methamphetamine intake [26]. This is evidenced in the human brain by reduced dopamine transporter density [27-31], which is correlated with psychiatric symptoms [29-31], motor anomalies [32] and memory impairment [32] in people who use the drug. Pre-treatment with NAC significantly attenuates the reduction in dopamine transporter density seen subsequent to high dose methamphetamine — this neuroprotective effect having been observed in mice [24], rats [33] and in non-human primates using positron emission tomography [25]. This evidence suggests that NAC could reduce neurotoxic damage in people using

methamphetamine and that it may also alleviate associated cognitive impairment and neuropsychiatric symptoms [14].

Human trials of NAC for addiction

So far there have been nine published trials in humans which together provide preliminary evidence of efficacy for NAC as a potential pharmacotherapy for addiction (Table 1).

Early trials examined effects on cocaine, initially showing a significant reduction in desire to use cocaine in an experimental setting, although no significant effects were observed for craving per se [34]. A subsequent open label trial on 23 people dependent on cocaine found promising results, with significant pre- vs. post- test reduction in cocaine use, craving for cocaine, abstinence symptoms and expenditure on cocaine [35]. A larger trial used a double-blind randomised control trial (RCT) to compare two dose conditions (1,200 mg per day (n = 40), or 2,400 mg per day (n = 33)) to a placebo (n = 38) [36]. This trial failed to find significant effects of either dose on cocaine use or craving. However, a post-hoc analysis of a subset of participants who were abstinent from cocaine at the start of the treatment found a significant reduction in craving with both 1,200 mg (n = 4) and 2,400 mg NAC per day (n = 8 cf. placebo, n = 5), and longer time to relapse with 2,400 mg NAC per day.

Similar lines of research have emerged examining the effect of NAC on cannabis [37,38] and nicotine dependence [39,40]. The largest trial conducted to-date (N = 116) found that 2,400 mg of NAC daily significantly reduced cannabis positive urines relative to placebo in an RCT [37]. Non-significant trends were observed for end of trial abstinence rates and survival to first cannabis positive urine, although the authors' note that the trial was not powered to detect these outcomes. Two small-scale but well controlled studies have looked at NAC

potential as a nicotine pharmacotherapy, and these have both found positive effects on smoking tobacco [39,40].

Only two trials to-date have examined the effect of NAC on methamphetamine dependence. The first of these trialled combined NAC with the opioid antagonist naltrexone (cf. placebo) making it hard to infer any effects of NAC per se [41]. The combination was not effective. A more recent randomised placebo-controlled cross over study (N = 23) conducted in Iran found that NAC significantly reduced craving for methamphetamine use in people seeking treatment for the drug. This study used 4 weeks of daily NAC dosing, starting at 600 mg per day for the first week, and increasing the dose to 1,200 mg per day for the subsequent 3 weeks. Over this time there was a gradual reduction in craving, with a large effect at 4 weeks relative to placebo. No other outcomes (eg, methamphetamine use or related comorbidities) were reported.

In none of these trials were there any reports of serious adverse events related to the use of NAC. Five trials have compared the prevalence of adverse effects with NAC to placebo and found no significant difference [36,40-43]. The small sample size in these studies means that they cannot provide definitive data on safety and tolerability, however, the results are consistent with several larger trials of NAC for psychiatric disorders [44-47] and the established safety profile of NAC in treating bronchopulmonary disorders [48], which indicates that side-effects are mostly gastrointestinal (nausea, vomiting, diarrhoea), self-limiting, and that serious side-effects are rare.

Considerations with the existing evidence-base

Most of the above trials (Table 1) were designed to assess feasibility and were not powered to test efficacy. None-the-less a number of them have provided signals of efficacy, including a well-controlled experimental study [34] and several RCTs [37,39,40,42]. Taken together these trials suggest that higher doses of NAC are more effective (e.g. 2,400 – 3,000 mg) and that these doses can be administered with a low risk of serious adverse effects. They also demonstrate that out-patient unsupervised dosing is feasible and that good compliance is achievable with this mode of delivery [36]. The effects of NAC in these human trials are consistent with the pre-clinical research, and suggest that NAC may reduce the risk of relapse by reducing desire to use a drug, with this effect possibly mediated by a decrease in craving.

Clearly there is a need to confirm positive effects of NAC (or null effects) with larger scale trials, particularly on various outcome measures (e.g., craving, use, abstinence symptoms) as effects on these different outcomes have not yet been consistently observed. This is true for both methamphetamine use and other drug types. A further consideration is in what context NAC may be most effective. Most trials have focussed on treatment seekers, and have included adjunctive psychosocial therapies, encouraged people to reduce their substance use or recruited participants who wished to reduce their substance use. It may be that NAC can facilitate recovery amongst those people already engaged in drug treatment, but it remains to be seen whether NAC may have a role amongst non-treatment seekers in reducing the severity of their substance use or related harms.

To-date there has been no consideration of the role of NAC in managing comorbid psychiatric symptoms, which may hinder treatment engagement and positive treatment outcomes, as well as being an independent source of morbidity. All but one trial limited

outcome measures to those directly related to drug use (e.g. days of use, clean urines, craving or abstinence symptoms), with this one trial finding a benefit for depressive symptoms but no change in disability [40]. The possibility that NAC could alleviate psychiatric symptoms is supported by its broader efficacy with other neuropsychiatric disorders (bipolar disorder depression, autism, schizophrenia), with NAC showing particular efficacy for depression [44-47,49]. In a pooled analysis of individuals with schizophrenia and bipolar disorder, NAC has also been found to alleviate memory impairments [50] and it has also been effective in preventing cognitive sequelae in victims of blast traumatic brain injury [51].

NAC's potential to alleviate psychiatric symptoms and neurocognitive disturbances is important in the context of methamphetamine use because around 40% of methamphetamine users experience psychotic symptoms like paranoia and hallucinations [52,53], symptoms of major depression are almost ubiquitous among treatment seekers [54] while heavy use dramatically increases the risk of hostility [55]. Methamphetamine use can also affect cognitive function [56], and this, along with other psychiatric disturbances, can impede engagement with psychosocial treatments and increase drop-out from treatment, resulting in poor outcomes [13]. As noted above, these neuropsychiatric and cognitive disturbances are at least in part mediated by the neurotoxic effects of methamphetamine which can be ameliorated by pre-treatment NAC. Therefore, NAC may have an important role to play in preventing the precipitation and exacerbation of methamphetamine-related neuropsychiatric and neurocognitive disturbances.

Conclusion

Together this evidence suggests that NAC may be helpful in managing symptoms of dependence that develop with heavy methamphetamine use (i.e. craving and relapse) and also

the specific pathologies that arise due to methamphetamine toxicity (e.g., paranoia, hostility and cognitive disturbances). However, the effects of NAC on methamphetamine craving need to be confirmed in full-scale trials, and its effects on other parameters, including methamphetamine use per se, and methamphetamine-related neuropsychiatric disturbances, needs to be examined. From such trials, it will be clearer what potential therapeutic role NAC could play in a clinical setting. NAC's potential ability to reduce craving and inhibit relapse may convey a benefit in reducing relapse rates post-rehabilitation, while NAC could also foreseeably help alleviate craving and depressive symptoms that are common during withdrawal. Among active methamphetamine users, NAC could have a potential harm-reduction role, helping people to manage their use and reducing the risk of neuropsychiatric sequelae that occur with heavy use. Even if these effects were modest, the relative ease with which NAC could be prescribed (as a take-home medication) may lead to a cost-effective reduction in the harms related to methamphetamine use at a population level. The generic effect of NAC on managing addiction across different drug types, ranging from cocaine to cannabis and tobacco [19,57], is a particular advantage over drug-specific agonist therapies: NAC may be helpful not only in managing methamphetamine dependence but also the high levels of poly-drug use seen among people dependent on the drug.

Acknowledgements: Nil.

Declaration of interest: Michael Berk has received grant support from Bristol- Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Meat and Livestock Board, Novartis, Mayne Pharma, and Servier; has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay, and Wyeth; and has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli

Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, and Servier. Other authors have no conflicts to declare.

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Table 1. Summary of human trials of NAC for addiction

Study	Participants	Active condition	Control	Study design	Outcome
LaRowe et al. 2007 [34]	15 cocaine dependent non-treatment seekers	1200 mg NAC for 2 days	Placebo	Double blind cross-over study	Reduced desire to use cocaine and reduced interest in cocaine; no significant effect on craving
Mardikan et al. 2007 [35]	23 cocaine dependent treatment seekers	1200, 2400 or 3600 mg NAC daily for 4 wks	Nil	Open label trial	Significant pre- vs. post-test reduction in cocaine use, expenditure on cocaine, craving and abstinence symptoms
LaRowe et al. 2013 [36]	111 cocaine dependent treatment seekers	1200 or 2,400 mg NAC daily for 8 wks + weekly CBT	Placebo + weekly CBT	Double-blind RCT	No effect on abstinence, craving or abstinence symptoms; significant craving and relapse reductions in initially abstinent participants ^b
Gray et al. 2010 [38]	24 cannabis dependent men interested in reducing use	2,400 mg NAC daily for 4 wks + encouraged to gradually reduce use	Nil	Open label trial	Significant pre- vs. post-test reduction in reported days of cannabis use & craving; no reduction in urine cannabinoid level ^a
Gray et al. 2012 [37]	116 cannabis dependent adolescents interested in treatment	2,400 mg NAC daily for 8 wks + wkly cognitive therapy	Placebo + wkly cognitive therapy	Double-blind RCT	Significantly reduced cannabis negative urines ^c
Knackstedt et al. 2009 [39]	29 nicotine dependent treatment seekers	2,400 mg NAC daily for 4 wks	Placebo	Double-blind RCT	Reduced cigarettes smoked; no change in CO ₂ , craving or withdrawal
Prado et al. 2015 [40]	34 tobacco (current smokers), treatment refractory	3,000 mg NAC daily for 12 wks+ monthly behavioural group sessions	Placebo	Double-blind RCT	Significant reduction in no. cigarettes/day, COEXH, depression symptoms & BMI; no effects on blood pressure or disability

Grant et al. 2010 [41]	31 methamphetamine dependent, non-treatment seekers	600-2,400 mg NAC + 50-200 mg naltrexone, incremental dosing over 6 wks ^d	Placebo	Double-blind RCT	No significant effect on craving or methamphetamine use
Mousavi et al. 2015 [42]	23 methamphetamine dependent treatment seekers	600-1,200 mg NAC daily incremental dosing + wkly group counselling	Placebo + wkly group counselling	Double-blind randomised cross-over study	Significantly reduced craving (only outcome reported)

^a Authors note limited utility of urinalysis data

^b Post-hoc exploratory analysis amongst a sub-set of patients abstinent from cocaine in the week prior to the trial (n = 17) revealed a significantly longer time to relapse with 2,400 mg NAC cf. placebo, significant reductions in craving for both NAC doses, with this effect being greatest for 2,400 mg.

^c Authors note a non-significant trend for abstinence at end of trial and survival to first cannabis positive urine and explain that the study was not powered to detect these outcomes

^d Dose not increased if significant clinical improvement was evident (no drug use and no urge to use).