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ABSTRACT

N-acetyl cysteine (NAC) is a widely available nutraceutical with a variety of actions. As a precursor of cysteine and glutathione, it has antioxidant properties that may impact on mood and contribute to an effect on impulsivity and obsessive behaviour. Via its additional effect on glutamate via the cystine-glutamate exchange system, NAC has been shown to mediate impulsivity in preclinical models of addiction, reduce craving, and cue extinction. Further, by boosting glutathione, NAC acts as a potent antioxidant and has been shown in two positive, large-scale randomized placebo-controlled trials to affect negative symptoms in schizophrenia and depression in bipolar disorder. We describe three cases in which its actions specifically on nail-biting and associated anxiety may offer a potential treatment. The spontaneous findings are reported as part of an ongoing treatment trial examining the utility of NAC in bipolar disorder. Its actions, if robustly replicated, also point to potential treatment targets in glutathione or glutamate pathways in the brain.

INTRODUCTION

Many findings in psychopharmacology are a result of clinical observation of serendipitous findings; this pattern is repeated in this case series. Pathological nail biting is a disorder that begins in adolescence and is regarded as a disruption of normal grooming behavio-
ior. This behavior is regarded as being in the compulsive-impulsive spectrum and is associated with psychological consequences including reduced self-esteem, as well as localized trauma and risk of infection. There is minimal data on the treatment of nail biting, with preliminary research suggesting that serotonergic agents may be of value, akin to other disorders in that spectrum such as compulsive skin picking and trichotillomania.

One safe and well-tolerated compound that offers some promise as a potential treatment in compulsive-impulsive disorders is N-acetylcysteine (NAC). NAC is widely available as a nutraceutical supplement and is an agent with multiple properties. It has an antioxidant action in its own right and influences neutrophil inhibition, antimicrobial attachment, vasodilation, and mucolysis. For over half a century it has been used therapeutically, traditionally as a mucolytic, in the treatment of paracetamol poisoning and most recently as a renal protectant.

Thus far, five cases of reduction in grooming disorders (trichotillomania, skin picking, and nail biting) with NAC have been reported, with a single case report describing its use in the treatment refractory of obsessive-compulsive disorder. NAC has also been demonstrated to be useful in other impulsivity related behaviours. Grant and colleagues gave open-labelled NAC (600–1,800 mg/day) to 27 subjects with pathological gambling, with 16 responders after 8 weeks of treatment. Studies by LaRowe and colleagues and Mardikian and colleagues suggest that NAC may be useful for the treatment of cocaine addiction.

This case series describes a reduction in nail biting reported spontaneously in the context of a clinical trial of add-on NAC for the treatment of bipolar disorder. It is noteworthy that nail biting was not a target of intervention in this trial and no behavioural suggestions were given that nail biting, or related behaviors, may be impacted by NAC treatment, reducing the likelihood of the observations being a halo effect.

CASE 1
A 46-year-old woman was first diagnosed with bipolar disorder following a suicide attempt at 17 years of age. She had no further problems until 34 years of age when her fourth child was born with a disability. She was working two jobs and her marriage fell apart. Since then she has been frequently depressed and had psychotic episodes. Presently she takes 900 mg of lithium and 300 mg of quetiapine daily.

At the first follow-up visit of the trial, 2 weeks after commencing on NAC 1,000 mg BID, she spontaneously reported that she had "stopped biting her nails". Seven months later, she has still not bitten them. Reviewing her nail-biting history she describes herself as a life long "nail biter" who has always had great difficulty in ceasing the habit. At 10 years of age her father offered her $1 for each nail she could grow, but she was unable to grow any. One month before her wedding, she did manage to stop, however, her nails did not grow much and were once again bitten off soon afterwards. In the past if she occasionally stopped nail biting for a short while her nails remained very soft, and bent and broke easily, especially along the ridges that grew into them. However on this occasion her nails have regrown strong and do not have any ridges. She stated that she had not consciously sought to stop biting them and it just happened.

CASE 2
A 44-year-old woman with symptoms of depression and anxiety for most of her life had suffered many major life events including abuse and violence between her parents and the deaths of two sisters due to a rare genetic disease. At 38 years of age she was diagnosed with rapid cycling bipolar disorder and put on a disability pension. She had a keen interest in natural therapies and took minimal medication. She was on mirtazapine 15 mg, fish oil, zinc, magnesium, vitamin B6, and valerian for sleeping.

Four months after starting on NAC 1,000 mg BID, she reported that she had ceased nail biting for the first time in a decade. Two months later, she had not resumed nail-biting even though she is a "lifelong nail biter", stating that everyone in her family does it and has only ever managed briefly to grow them for cosmetic reasons at 20 years of age. She is very aware of the link between stress and nail biting. Since commencing on NAC she has felt relaxed enough to consciously stop biting them. She initially noticed that one nail had grown and consequently focused on stopping biting the remainder.
CASE 3
A 46-year-old man who had experienced depressive and manic symptoms from 16 years of age was first diagnosed with bipolar disorder at 45 years of age. In the past he had been hospitalized three times for depression and had tried medication but found the weight gain side effects intolerable. He had a family history of depression on his maternal side but none of his immediate family had significant psychological disorders. He also described obsessional thinking concerning exercise and diet, and had a longstanding habit of chewing on his nails and the surrounding skin of his fingers.

After participating in the NAC trial for 28 weeks he reported that he had noticed a reduction in his nail-biting behavior. He was not sure when his nail-biting had begun to diminish as it had not been the result of a conscious decision to alter his behavior.

DISCUSSION
NAC has two major mechanisms that mark it as an agent of potential value in disorders in the compulsive-impulsive spectrum. Firstly, glutamate, and in particular the cystine-glutamate exchange system, has been shown to mediate impulsivity in preclinical models of addiction, and NAC has been shown to reduce craving and cue extinction in animal models of both cocaine and opiate dependence.\(^\text{10}\) Secondly, NAC, by boosting glutathione, is a potent antioxidant, and has been shown in two positive, large-scale randomized placebo-controlled trials\(^\text{11,12}\) to potentially affect substance use in schizophrenia and in bipolar disorder. NAC's benefit on depression in bipolar disorder suggests that its role in dysphoric mood states may positively affect compulsive-impulsive behaviors.\(^\text{10}\)

The nucleus accumbens is a key region implicated in impulsivity where basal levels of extracellular glutamate are maintained primarily by the exchange of extracellular cysteine for intracellular glutamate. The cysteine glutamate exchange system is ubiquitous in the brain and has a further role in protecting against oxidative stress by providing the rate-limiting factor for glutathione synthesis, cysteine.\(^\text{13}\)

Glutathione is a free radical scavenger. An excess of reactive oxygen species may cause persistent reduction in cystine-glutamate exchange in the nucleus accumbens, which may contribute to pathological glutamate signaling. The effects of glutamate in the nucleus accumbens are mediated by group II metabotropic glutamate autoreceptors. NAC increases extracellular levels of glutamate, which stimulates group II metabotropic glutamate receptors. Increasing glutamate in the nucleus accumbens has been shown to reduce impulsivity in models of compulsive drug-seeking behaviors. McFarland and colleagues\(^\text{14}\) found in a rat model of cocaine addiction that drug-seeking behavior was mediated by prefrontal glutamate release into the nucleus accumbens. In line with this, NAC prevented escalation of drug intake and behavioral sensitization in an animal model of cocaine addiction.\(^\text{15}\) Further, group II metabotropic glutamate receptor agonists inhibited the reinstatement of cocaine- or heroin-seeking behavior, suggesting that this effect is mediated via group II metabotropic receptors.\(^\text{16,17}\) Baker and colleagues\(^\text{18}\) have also demonstrated that re-instatement of drug seeking behavior can be prevented by stimulating cysteine glutamate exchange by NAC in a cocaine model of addiction. Similarly, Zhou and Kalivas\(^\text{19}\) showed that NAC blocks heroin-induced reinstatement behaviour and cue responsivity, suggesting that this mechanism plays an important role in the reward circuitry in addictive states. Consequently, NAC treatment may be able to restore extracellular glutamate in the nucleus accumbens, which may inhibit compulsive behaviors.\(^\text{7}\)

There is clinical data that supports this hypothesis. Mardikian and colleagues\(^\text{20}\) showed that NAC reduced cocaine use in an outpatient cohort and there was a suggestion of greater utility of higher doses (2,400 mg and 3,600 mg) than lower (1,200 mg) doses. LaRowe and colleagues\(^\text{21}\) similarly found that NAC was superior to placebo for reducing ratings of desire to use cocaine and reduction in responsivity to cocaine cues in people with cocaine dependence. Grant and colleagues\(^\text{22}\) found that NAC was superior to placebo for symptom reduction in pathological gambling, suggesting a key mediating role of glutamate in non-pharmacological addictions and of NAC in the remediation of such behavior.

In addition to impacting upon impulsivity and addictive cues, NAC may also vary other responses through glutathione. In animal models it has been shown that distinct signaling pathways modulate glutathione metabolism contingent upon whether cortical neurons are stressed or unstressed.\(^\text{23}\)
CONCLUSION

The exact mechanism of action of NAC in these three cases, via a direct pathway or via an effect on stress and anxiety, remains to be elucidated. However, a potential role of NAC in nail-biting is suggested. Trials examining this condition as well as related disorders in the obsessive-compulsive spectrum may be valuable and this is of particular importance as effective treatments are not currently available. If replicated, these cases implicate additional mechanisms in the pathophysiology of such disorders, including the role of glutamate and cysteine-glutamate exchange, as well as oxidative stress.

REFERENCES

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