



The Potential of N-Acetylcysteine for Treatment of Trichotillomania, Excoriation Disorder, Onychophagia, and Onychotillomania

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Body Focused Repetitive Behaviors

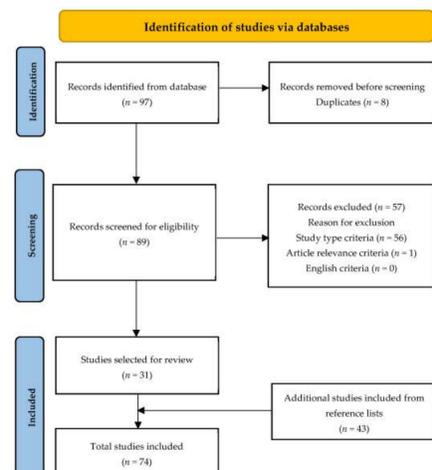
- Trichotillomania (hair pulling), excoriation disorder (skin picking), onychophagia (nail biting), and onychotillomania (nail picking) are body focused repetitive behaviors (BFRBs) causing damage to skin, hair, and nails, often with clinically significant **psychosocial consequences**.
- BFRBs are associated with **neuropsychiatric comorbidities**.
- There are currently **no standardized treatment** for BFRBs.
- Psychotropic drugs (SSRIs, anticonvulsants, tricyclic antidepressants) have been studied with variable efficacy.
- Pathophysiology is incompletely understood, though hyperactivity due to increased glutaminergic excitation or reduced GABAergic inhibition has been hypothesized.

N-Acetylcysteine (NAC)

- N-acetylcysteine (NAC) is a glutamate modulator and antioxidant that has shown promise in reducing compulsive behaviors in BFRB.
- NAC is inexpensive and available as an over-the-counter supplement.
- NAC has a benign side effect profile.

Methods

- A literature search for peer-reviewed articles using the PubMed/MEDLINE database was conducted in March 2022.
- A total of 74 articles were included in the review.



Results

Figure 1. NAC treatment studies for trichotillomania

Table 1. Summarizes all NAC treatment studies for TTM, which includes one adult and one pediatric randomized double-blind controlled trials and nine case reports.

Study	Design	Patients	Age (Year)	Comorbidities	NAC Dose	Other Concurrent Medications	Outcomes
Grant, Odlaug, and Kim (2009) [30]	RDBPCT	Adult (n = 50)	18-65	Depression, anxiety, OCD, PTSD, SPD, bulimia	1200-2400 mg/day	SSRIs, SNRIs, stimulants, psychotherapy	The NAC group showed higher efficacy ($F_{1,47} = 32.152, p < 0.001$) compared to the placebo group based on MGH-HPS. The NAC group also showed improvement in hair pulling severity ($F_{1,47} = 18.245, p < 0.001$) and resistance and control ($F_{1,47} = 37.067, p < 0.001$) compared to placebo.
Bloch et al. (2013) [11]	RDBPCT	Pediatric (n = 39)	8-17	ADHD, depression, anxiety, OCD, tic disorder, SPD	600-2400 mg/day	SSRIs, antipsychotics, stimulant, psychotherapy	No significant difference between NAC and placebo group based on MGH-HPS ($p = 0.55$). Moderate decrease in hair pulling noted in both groups ($p = 0.002$).
Zhao et al. (2021) [13]	Case report	Adult (n = 1)	25, F	BED, anxiety, depression	600-1800 mg/day	Fluvoxamine 150 mg/day, bupropion 300 mg/day	After 2 weeks, stable mood and reduced hair pulling behavior reported. At 14 weeks, patient reported no hair pulling or binge eating episodes, and improved anxiety and depression.
Jones, Keuthen, and Greenberg (2018) [34]	Case report	Adult (n = 1)	18, F	OCD, depression, anxiety, SPD	2700 mg/day	Fluoxetine 40 mg/day, psychotherapy	After 16 weeks, patient showed significant reduction in hair pulling, skin picking, depression, anxiety, and OCD symptoms. Full remission was not reached.
Kilic and Koles (2018) [5]	Case report	Adult (n = 1)	18, F	Depression, anxiety	1200 mg/day	Fluoxetine 40 mg/day	After 3 weeks, patient showed decreased hair pulling urges and behavior. All depression and anxiety symptoms ceased. At 6-month follow-up, no hair pulling was noted.
Pino et al. (2017) [36]	Case report	Pediatric (n = 1)	12, F	Not specified	2400 mg/day	Doxepin 10 mg/day, fluoxetine 20 mg/day, pimevide 2 mg/day	After 6 months, patient had improved hair density and dermopathy findings.
Burroso et al. (2017) [37]	Case report	Pediatric (n = 1)	11, M	Asthma, atopic dermatitis	1200-1800 mg/day	None	After 3 months, patient showed improvement at 1200 mg/day. Remission with complete hair regrowth was achieved at 1800 mg/day for 3 months.
Ozcan and Seckin (2016) [38]	Case report	Adult and pediatric (n = 2)	30, F; 14, F	Not specified; ADHD	1200 mg/day	None; methylphenidate	Case 1: After 2 months, hair pulling decreased with complete remission within 4 months. No recurrence of hair pulling was noted at 7-month follow-up. Case 2: After 2 weeks, significant improvement of hair pulling noted with complete hair regrowth after 6 months. No recurrence of hair pulling noted at 8-month follow-up.
Taylor and Sibaprasadas (2014) [39]	Case report	Adult (n = 1)	58, F	Unexplained weight loss	1200 mg/day	None	After 4 weeks, patient showed noticeable regrowth of hair, which further improved at 10 weeks. Progress continued and maintained at 12 weeks.
Rodriguez Barata et al. (2012) [40]	Case report	Adult (n = 2)	23, F; 19, F	Alopecia; Not specified	1200 mg/day	None	Case 1: Within 2 months, hair regrowth was observed; Case 2: Complete regrowth was observed after 3 months of treatment.
Odlaug and Grant (2007) [41]	Case report	Adult (n = 2)	28, M; 40, F	ADHD, nail biting; Not specified	600-1800 mg/day; 600-2400 mg/day	None	Case 1: Dose was increased from 600 to 1800 mg/day over several weeks. Complete cessation of pulling after 1 week on 1800 mg/day. Case 2: Dose was increased from 600 to 2400 mg/day. Complete cessation of urges and hair pulling after 2 weeks on 2400 mg/day.

NAC, N-acetylcysteine; RDBPCT, randomized double blind placebo controlled trial; ADHD, attention deficit hyperactive disorder; OCD, obsessive-compulsive disorder; SPD, skin picking disorder; TTM, trichotillomania; PTSD, post-traumatic stress disorder; BED, binge eating disorder; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MGH-HPS, Massachusetts General Hospital-Hair Pulling Scale; NE-YBOCS, Yale-Brown Obsessive Compulsive Scale; CGI, Clinical Global Impression.

Figure 2. NAC treatment studies for excoriation disorder

Table 2. Summarizes all NAC treatment studies for excoriation disorder, which includes one adult randomized double-blind controlled trial, two adult retrospective cohort studies, one adult and pediatric open-label pilot study, and five case reports.

Study	Design	Patients	Age (Year)	Comorbidities	NAC Dose	Other Concurrent Medications	Outcomes
Grant et al. (2016) [46]	RDBPCT	Adult (n = 66)	18-65	Depression, anxiety, TTM, nail biting	1200-3000 mg/day	Psychotropic medications	After 12 weeks, NAC treatment group showed significant improvement in skin picking severity compared to placebo based on NE-YBOCS and CGI Severity scale ($p = 0.008, p = 0.019$).
Hwang, Campbell, and Sartori-Valocchi (2021) [47]	Retrospective cohort study	Adult (n = 28)	Mean: 57.2	Not specified	1200-2400 mg/day	Doxepin, duloxetine	After 12 weeks, 61.5% of patients reported a positive response to NAC.
Miller and Angulo (2013) [48]	Open-label pilot study	Adult and pediatric (n = 35)	5-39	Prader-Willi syndrome	450-1200 mg/day	Valproic acid, quetiapine, risperidone, spiroperone, growth hormone, metformin, levotyrosine, modafinil	After 12 weeks, 100% of patients reported reduced skin picking behavior and 71% achieved complete resolution.
Wieting et al. (2021) [49]	Retrospective cohort study	Adult (n = 14)	17-53	Prader-Willi syndrome	1800-2400 mg/day	Risperidone, pipamperone, aripiprazole, sertraline, mirtazapine	After 12 weeks, 6 patients reported no changes in symptoms and 2 had worsened symptoms based on CGI improvement scale.
Ozcan (2021) [50]	Case report	Adult (n = 2)	75, F; 36, F	Not specified	1200 mg/day	None	Case 1: After 2 weeks, patient reported decreased skin picking. Treatment was continued for 3 months and no relapse at 6-month follow-up. Case 2: After 6 weeks, complete cessation skin picking reported and no relapse at 3-month follow-up.
Kilic and Koles (2019) [5]	Case report	Adult (n = 1)	42, F	Depression	1200 mg/day	Venlafaxine 225 mg/day	After 10 days, patient reported decreased skin picking symptoms. Complete cessation of skin picking achieved at 3 months.
Silva-Netto et al. (2014) [51]	Case report	Adult (n = 3)	45, F; 40, F; 31, F	TTM, depression, Bipolar disorder, Depression, pathological jealousy, internet addiction	1200-1800 mg/day; 1200 mg/day; 1200 mg/day	Venlafaxine 75 mg/day; lithium 600 mg/day; quetiapine 50 mg/day; fluoxetine 20 mg/day	Case 1: Skin picking resolved completely. Case 2: Complete resolution of skin picking achieved and maintained for 10 months. Case 3: Substantial improvement of skin picking.
Perechal and Yazici (2014) [52]	Case report	Pediatric (n = 1)	12, F	Not specified	600-1800 mg/day	None	4 weeks after a dose increase from 600 to 1200 mg/day, skin picking urges and behavior decreased dramatically and complete remission achieved after 4 weeks on 1800 mg/day.
Odlaug and Grant (2007) [41]	Case report	Adult (n = 1)	52, F	Bulimia nervosa, compulsive buying	600-1800 mg/day	None	Patient reported 50% decrease of picking urges and behaviors within 1 week after dose increase from 600 to 1200 mg/day. Patient had no skin picking behavior after a dose increase to 1800 mg/day.

NAC, N-acetylcysteine; RDBPCT, randomized double blind placebo controlled trial; ADHD, attention deficit hyperactive disorder; OCD, obsessive-compulsive disorder; SPD, skin picking disorder; TTM, trichotillomania; PTSD, post-traumatic stress disorder; BED, binge eating disorder; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MGH-HPS, Massachusetts General Hospital-Hair Pulling Scale; NE-YBOCS, Yale-Brown Obsessive Compulsive Scale; CGI, Clinical Global Impression.

Figure 3. NAC treatment studies for onychophagia

Table 3. Summarizes all NAC treatment studies for onychophagia, which includes one pediatric randomized double-blind controlled trials and three case reports.

Study	Design	Patients	Age (Year)	Comorbidities	NAC Dose	Other Concurrent Medications	Outcomes
Ghanizadeh et al. (2013) [53]	RDBPCT	Pediatric (n = 42)	6-18	OCD, depression, anxiety, ADHD, tic disorder, SPD	200-800 mg/day	SSRIs, SNRIs, stimulants, antipsychotics, TCAs	Significantly increased nail length in treatment group compared to placebo after 1 month ($p < 0.01$). No significant difference noted after 2 months.
Kilic and Koles (2019) [5]	Case report	Adult (n = 1)	24, M	Not specified	1200-1800 mg/day	None	After 3 weeks on 1800 mg/day, patient lost urge to bite his nails. Efficacy was maintained after 6 weeks.
Ghanizadeh and Derakhshan (2012) [59]	Case report	Pediatric (n = 1)	8, M	Autism	800 mg/day	Risperidone 2 mg/day and thioridazine 10 mg/day	After 1 month of NAC, patient's parents reported reduced nail biting and autism symptoms.
Berk et al. (2009) [60]	Case report	Adult (n = 3)	46, F; 44, F; 46, M	Bipolar disorder; Depression, anxiety; bipolar disorder; Depression, bipolar disorder	2000 mg/day; 2000 mg/day; Not specified	Lithium 900 mg/day, quetiapine 300 mg/day, Mirtazapine 15 mg/day	Case 1: After 2 weeks, patient completely stopped nail biting and results were maintained at 7-month follow-up; Case 2: After 4 months, patient completely stopped nail biting and results were maintained at 2-month follow-up; Case 3: After 28 weeks, patient reported reduction in nail biting.

NAC, N-acetylcysteine; RDBPCT, randomized double blind placebo controlled trial; ADHD, attention deficit hyperactive disorder; OCD, obsessive-compulsive disorder; SPD, skin picking disorder; TTM, trichotillomania; PTSD, post-traumatic stress disorder; BED, binge eating disorder; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MGH-HPS, Massachusetts General Hospital-Hair Pulling Scale; NE-YBOCS, Yale-Brown Obsessive Compulsive Scale; CGI, Clinical Global Impression.

Discussion

- Numerous studies have assessed the efficacy of NAC for BFRBs.
- **Effective dose of NAC is uncertain** as many studies used varying dosages, especially in pediatric v. adult populations.
- Some studies may have used subtherapeutic dosages, which may have affected results.
- It remains unclear if higher doses correlate with greater efficacy.
- **Medication adherence** was not emphasized in most studies.
- NAC has **limited bioavailability** which may be a limitation for efficacy.
- There is evidence that esterification of the carboxyl group in NAC to produce N-acetylcysteine ethyl ester (NACET) increases lipophilicity with improved pharmacokinetics.

Conclusions

- NAC may be a promising treatment for BFRBs with **high efficacy, low side effect profile, and affordability**.
- Evidence is limited, with only 2 clinical trials for trichotillomania, one clinical trial for excoriation disorder, one trial for onychophagia, and none for onychotillomania.
- **Long-term clinical trials with larger sample sizes** for adult and pediatric populations are needed.

References

- Wu, K.; Hanna, G.L.; Rosenberg, D.R.; Arnold, P.D. The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder. *Pharmacol. Biochem. Behav.* 2012, 100, 726–735.
- Smaga, I.; Frankowska, M.; Filip, M. N-acetylcysteine as a new prominent approach for treating psychiatric disorders. *Br. J. Pharmacol.* 2021, 178, 2569–2594.