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**SYSTEMATIC REVIEW ARTICLE**

# Drug Treatment of Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-picking) Disorder, and Nail-biting (Onychophagia)

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**Abstract:** ***Background*:** Trichotillomania (TTM), excoriation (or skin-picking) disorder and some severe forms of onychophagia are classified under obsessive-compulsive and related disorders. There are different interacting neurotransmitter systems involved in the pathophysiology of impulse-control disorders, implicating noradrenaline, serotonin, dopamine, opioid peptides and glutamate, hence investigators focused on drugs able to act on these transmitters. Our aim was to critically review the efficacy of the drugs employed in impulse-control disorders.

***Methods*:** We searched for controlled drug trials to treat TTM, excoriation, and/or nail-biting six databases (PubMed, Cochrane, Scopus, CINAHL, PsycINFO/PsycARTICLES, and Web of Science), using the search strategy: (trichotillomania OR "excoriation disorder" OR "face picking" OR "skin picking" OR "hair pulling" OR onychophagia OR "nail-biting") AND drug treatment on 12 March 2018 for all databases. We followed in our method of identifying relevant literature the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (*PRISMA*) statement.

***Results*:** SSRIs and clomipramine are considered first-line in TTM. In addition, family members of TTM patients are often affected by obsessive-compulsive spectrum disorders. Other drugs used in the treatment of TTM are lamotrigine, olanzapine, N-Acetylcysteine, inositol, and naltrexone.

***Conclusion*:** The treatment of TTM, excoriation disorder and nail-biting is still rather disappointing. Conjectures made from preclinical studies and the relative pathophysiological hypotheses found poor confirmations at a clinical level. There is a need for further studies and the integration of pharmacological and psychotherapeutic. Our results point to the need of integrating personalised medicine principles in the treatment of these patients.

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## 1. INTRODUCTION

Trichotillomania (also known as a hair-pulling disorder, TTM), excoriation (or skin-picking) disorder and some severe forms of onychophagia (nail-biting) are classified under obsessive-compulsive and related disorders in the American Psychiatric Association's (APA)-DSM-5 [1]. The APA DSM-5 Task Force decided to pull-out obsessive-compulsive disorder (OCD) from the chapter on anxiety disorders and to create a brand new chapter, obsessive-compulsive and related disorders, flanking it by other disorders that could be related to one another in terms of diagnostic validators and clinical affinity. Thus, they pooled out hoarding disorder from OCD and put it as a self-standing disorder, created substance-/medication-induced obsessive-compulsive and related disorder, and obsessive-compulsive and related disorder due to another medical condition while moving trichotillomania (hair-pulling disorder, TTM) and excoriation (skin-picking) disorder the DSM-IV impulse-control disorders to the OCD spectrum. While onychophagia is currently an ill-defined diagnostic entity, TTM and skin picking disorder have their own diagnostic criteria in the latest version of the manual. However, there are three features that all these three entities share: a) continuous repetition of a specific behaviour (*i.e.*, tearing-off hair in TTM, skin picking in excoriation disorder, and nail-biting in onychophagia; b) repeated attempts to reduce or eliminate the behaviour (recognised as dysfunctional); and c) clinically significant impairment on the psychological, social, and occupational levels. Lip chewing is also considered along this spectrum, but

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its occurrence is so rare outside from the genetically determined Lesch-Nyhan syndrome, that no randomised clinical trials (RCTs) have dealt with its drug treatment to date. In this review, we will not focus on other Obsessive-Compulsive and Related Disorders (OCD spectrum), like body dysmorphic, hoarding, substance/medication-induced, other specified and unspecified disorders or OCD spectrum disorder due to another medical condition, nor will we deal with impulse control disorder like fire setting (pyromania) or shop-lifting (kleptomania) (both currently grouped under the umbrella term "disruptive, impulse-control, and conduct disorders"). The reason for this exclusion is that all these conditions do not involve a *direct* self-inflicted damage to one's own body with no suicidal intent, whereas self-cutting in the context of borderline personality disorder is not comprised among OCD spectrum disorders, despite bearing commonalities.

Although TTM, pathological skin picking and nail biting have lately been receiving growing scientific attention in animal research, especially in rodents, there still are very few studies on humans [2]. The prevalence of these disorders in humans ranges between 0.5% and 2% for TTM [3] and 1.4% and 5.4% for excoriation disorder [4]. In 2013 DSM-5 [1], onychophagia (nail biting) is lumped in the context of the obsessive-compulsive spectrum disorders along with lip biting and cheek chewing within "body-focused repetitive behaviour disorder" for which it does not provide clear-cut diagnostic criteria. Its prevalence in the general population is also unclear, as the nail-biting behaviour is very common but does not always qualifies for onychophagia, unless there are repeated attempts to decrease or stop the behaviour, that causes clinically significant reduction of functioning (social, occupational, or other) distress or impairment not better explainable by hair-pulling or skin-picking disorders, stereotypic behaviour, or non-suicidal self-injury. Its prevalence is estimated to be approximately 50% in childhood [5] and decreases to about half that figure around 17-18 years [6], although the behaviour may persist in adulthood, and one study found that 4.5% of people in their 60s had retained the habit [7].

Regarding gender differences, TTM and skin picking disorder affects women more than men (3:1) [8, 9], as also does onychophagia, although to a lesser extent (1.5:1) [10]. Perseverating in such pathological behaviours may lead to general medical problems (*e.g*., irreversible hair loss, irreversible skin lesions such as keloids, dental problems, and infectious complications) thus adding to the existing psychological distress. Various interventions have been proposed to manage this disorder, mainly behavioural (psychotherapy, hypnosis, and a series of behavioural treatments) but their use has shown limited effectiveness. On the other hand, randomised controlled trials on possible drug treatments are few and currently, there is no drug approved by the US American Food and Drug Administration for these disorders.

There are different interacting neurotransmitter systems involved in the pathophysiology of impulse-control disorders, implicating noradrenaline, serotonin, dopamine, opioid peptides [11] and glutamate [12, 13], hence investigators focused on drugs able to act on these transmitters. Our aim was to critically review the efficacy of the drugs employed in impulse-control disorders by searching six databases for randomized controlled drug trials on either TTM, excoriation or nail-biting disorder.

## 2. METHODS

We searched for controlled drug trials to treat TTM, excoriation, and/or nail-biting six databases, using the search strategy: (trichotillomania OR "excoriation disorder" OR "face picking" OR "skin picking" OR "hair pulling" OR onychophagia OR "nail-biting") AND drug treatment on 12 March 2018 for all databases. We followed in our method of identifying relevant literature the *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (*PRISMA*) statement [14]. All authors considered every single record for inclusion and agreed on their relevance to our goals. Our goal was to identify double-blind trials of drugs used to treat excoriation disorder, TTM, or nail-biting that satisfied minimum quality criteria (*i.e*., randomisation, parallel design, adequate observation time and dosing, clear-cut diagnostic criteria, and clinical efficacy and safety outcomes). Exclusion criteria were reviews, open trials, editorials/opinion papers/views, animal studies, non-peer reviewed abstracts from conferences/congresses, and case reports (but their reference lists were searched for possible other undetected studies that could meet our inclusion criteria). Inclusion followed a Delphi procedure carried out by all authors. There were as many rounds there were needed until unanimity was reached. In case of lack of universal consensus, it had been decided that it was supervisor GDK who had to resolve the dispute, but in no case did this become necessary.

## 3. RESULTS AND DISCUSSION

The search conducted on 12 March 2018 produced 288 records on PubMed, 37 on Cochrane, 75 on Scopus, 2 on CINAHL, 22 on PsycINFO/PsycARTICLES, and 72 on Web of Science, totalling 401 records after removal of duplicates. Results are shown in Fig. **1**. Of the initially identified records, 389 studies were excluded, thus leaving for further comment the 12 studies shown in Table **1**. No further studies were identified through the reference lists of the excluded papers. Reasons for exclusion are shown in the *PRISMA* flow-diagram in Fig. **1**. We will here discuss included papers according to the drug class of the tested drugs.

### 3.1. Antidepressants

SSRIs and clomipramine are considered first-line in TTM, probably due to the high rate of comorbidity that exists with obsessive-compulsive and related disorders. In addition, family members of TTM patients are often affected by obsessive-compulsive spectrum disorders, indicating a possible common aetiology and genetic predisposition.

Clomipramine is a tricyclic antidepressant (TCA) that blocks the reuptake of noradrenaline and serotonin in the synaptic gap; it also blocks muscarinic cholinergic, adrenergic, histamine $H_1$ and 5-$HT_2$ serotonergic receptors. Clomipramine has a particular tricyclic profile that makes it much more similar to SSRIs, thanks to its potent inhibition of serotonin reuptake. Due to its pharmacological profile, it has

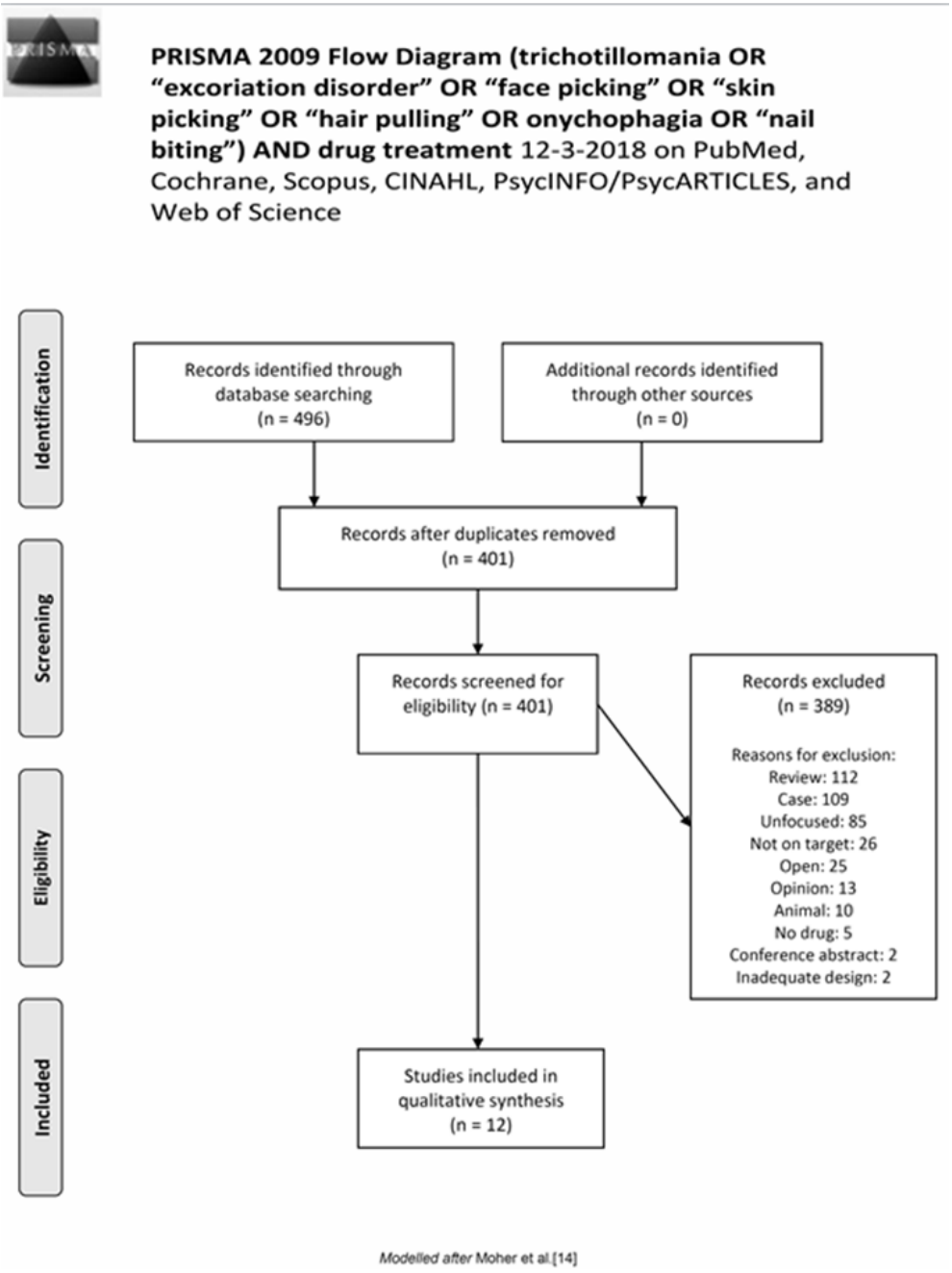


**Fig. (1).** PRISMA search strategy and results, including reasons for exclusion.

been widely used in the treatment of obsessive-compulsive disorder (OCD). On the other hand, its effectiveness in TTM is yet to be proven.

In a double-blind study that compared clomipramine at the flexible dosage (6 patients) with placebo (5 patients) and cognitive-behavioral therapy with 45-minute weekly sessions (5 patients), both clomipramine and CBT showed efficacy in reducing the severity of hair pulling but only the latter had statistical significance [15]. It should be noted that patients who received clomipramine took the drug at an average dose of 116.7 mg/day, a dose with proven antidepressant efficacy, but certainly lower than what is usually given to patients with OCD. This study used the double-blind design for the placebo *vs*. clomipramine arms but obviously could not do this for CBT; however, the rater of the patients' conditions was blind as to the treatment they were receiving, thus ensuring a certain degree of objectivity. The main criticism regards the dosage of clomipramine used.

Another clomipramine study compared it with another TCA with a more noradrenergic profile, desipramine [16]. In this double-blind crossover study, 13 patients were given, after a two-week single-blind placebo phase intended to exclude patients responding to placebo by as little as 20%, clomipramine (mean dose = 180.8 mg/day) or desipramine (mean dose = 173.1 mg/day) in a double-blind manner for 5 weeks, thereafter each group switching to the other drug.

**Table 1. Summary of studies conducted on trichotillomania, excoriation (skin picking) disorder and nail biting (onychophagia).**

| Study | Population | Design | Results | Conclusion |
|---|---|---|---|---|
| Swedo *et al*., 1989 [19] | 13 pts with DSM-III-R trichotillomania | Double-blind crossover study of clomipramine (mmd ± SD, 180.8 mg/day ± 56.0) *vs*. desipramine (173.1 mg/day ± 33) × 10-wk (5-wk clomipramine + 5 wk desipramine) after 2 wk single-blind placebo; Assessment: BL and weekly to 16 wk EP | Clomipramine was clearly superior to desipramine in the treatment of trichotillomania. Clomipramine resulted in a significantly greater overall improvement in severity of trichotillomania than desipramine, as measured by the TIS ($p$=0.03). One patient developed unnamed, poorly tolerable side effects and was switched to fluoxetine | Clomipramine better than desipramine for the short-term treatment of trichotillomania |
| Leonard *et al*., 1991 [17] | 14 pts with severe morbid onychophagia (and no history of OCD) | Double-blind crossover study of clomipramine (mean ± SD dose, 120 mg/day ± 48) *vs*. desipramine (135 mg/day ± 53) × 10 weeks (5 wks clomipramine + 5 wks desipramine) after 2-week single-blind placebo; assessment with the Nail Biting Severity, Nail Biting Impairment, and Clinical Progress Scales at BL and weekly to 12 wk EP | > ↓ in onychophagia during clomipramine than with desipramine as measured on the Nail Biting Severity (F = 3.75, df=1,12, $p$<0.04), the Nail Biting Impairment (F = 5.27, df = 1,12, $p$<0.02), and the Clinical Progress (F = 7.65, df = 1,12, $p$<0.01) scales. Side effects were for clomipramine-desipramine dry mouth (12-8), fatigue (10-5), insomnia (7-10), constipation (6-7), sweating (6-5), and dizziness (5-3) | The 14 completers had > improvement of their onychophagia with clomipramine than with desipramine, as measured on three clinical nail biting scales |
| Christenson *et al*., 1991 [22] | 14 pts with DSM-III-R trichotillomania | Double-blind crossover study of fluoxetine (doses up to 80 mg/day) *vs*. placebo × 18 wks (6-week trials of each agent separated by a 5-week washout period); Assessment: HDRS, BDI, number of hair-pulling episodes/wk, estimated number of hairs pulled/wk, counted number of hairs pulled/wk, weekly subject rating of severity of the urge to pull-out hair, weekly subject rating of the severity of hair pulling | No significant treatment type×time interactions for all measures (subject ratings of hair pulling/wk, subject ratings of the urge to pull hair/wk, assessments of the number of hair-pulling episodes per week, estimated amount of hair pulled/wk). Side effects with placebo similar to fluoxetine (nausea 31.3%; tremor, insomnia, dry mouth, urinary hesitancy, irritability, and sedation 12.5%, hot flashes, yawning, anorgasrnia, and sweating 6.3%) | Fluoxetine did not prove to be an effective short-term treatment of trichotillomania |
| Streichenwein & Thornby, 1995 [23] | 16 pts with DSM-III-R trichotillomania (SCID-R) | Double-blind, cross-over fluoxetine (15 pts reached 80 mg/day, 1 pt stayed at 60 mg/day) *vs.* placebo × 31 wks (initial 2-week placebo washout; 12-wks with either fluoxetine or placebo; 5-wk washout with no capsules; → crossover to other treatment for additional 12 wks); weekly assessment: HDRS, BDI, VAS scores (0-10) of subjects' self-ratings of the severity of hair pulling urge and number of episodes; daily hair counts and number of days of hair pulling | No variable (severity rating of hair pulling and urge, estimated hair loss, hair-pulling episodes) showed significant weekly improvement. No significant differences between placebo and fluoxetine. Adverse effects fluoxetine-placebo: nightmares, insomnia, dizziness, irritability, anxiety, doom feeling (22-16); anorexia, diarrhoea, constipation, nausea, increased weight, abdominal pain, dyspepsia (14-5); anorgasmia, decreased libido (2-0); and chest pain (0-1) | Fluoxetine seems not to be an effective treatment of trichotillomania |
| Ninan *et al*., 2000 [15] | 16 pts with DSM-III-R trichotillomania (SCID-R) | Double-blind clomipramine (N=6, flexible dosage, mean dose of 116.7 mg/day) *vs*. CBT (N=5, weekly 45-minute session) *vs.* placebo (N=5) × 9 wks; Assessment: TSS, TIS, CGIi, weekly from BL to EP | Severity ($p$=0.002) and impairment ($p$=0.006) were significantly reduced. CBT produced significantly more change ($p$<0.05) than placebo or clomipramine. Responders to CBT were significantly higher than for clomipramine ($p$=0.016) and placebo ($p$=0.026). Clomipramine-responders were more than placebo-responders, but not significantly so ($p$=0.061). Side effects, fluoxetine: tremor (3), sedation, dry mouth, constipation (2 each), memory difficulty, nausea (1 each); placebo: increased appetite (1) | CBT and clomipramine were both effective in reducing severity in hair pulling (no significant benefit with placebo), but CBT significantly prevailed over both |
| Grant *et al*., 2009 [30] | 50 pts with DSM-IV trichotillomania | Double-blind *N*-acetylcysteine (N=25, 1200 mg/day. At wk 6, dose was ↑ to 2400 mg/day × remaining 6 wks of the study) *vs.* placebo (N=25) ×12 wks; Assessment at BL every 3 wk × 12 wk (primary outcome: MGH-HPS; secondary: PITS, CGIs, CGIi, SDS, QoLI, HARS, HDRS) | Significantly better results on MGH-HPS, PITS, CGIi, CGIs in *N*-acetylcysteine compared with placebo. No significant differences between the two groups in SDS total score and QoLI. No adverse events in *N*-acetylcysteine group, mild in placebo group | *N*-acetylcysteine is safe and more effective than placebo for trichotillomania, showing beneficial effects within 9 wk from treatment initiation |

**(Table 1) contd….**

| Study | Population | Design | Results | Conclusion |
|---|---|---|---|---|
| Van Ameringen *et al*., 2010 [53] | 25 pts with DSM-IV trichotillomania | Double-blind olanzapine (N=13, flexible dosage, mean dose of 10.8mg/die) *vs*. placebo (N=12) × 12wk; Assessment (primary outcome: CGIi; secondary: TTM-YBOCS, CGIs, MGH-HPS, QoL-ESQ, BDI, BAI, SDS) from BL q 2wk to EP | Significant improvement of CGIi, CGIs and significant reduction of TTM-YBOCS scores in olanzapine group compared with placebo. Adverse events, olanzapine-placebo: dry mouth 54%-0%, fatigue 54%-0%, increased appetite 46%-0%, headache 38%-33%, and weight gain 38%-8% | Olanzapine seems an effective and safe treatment for trichotillomania |
| Grant *et al*., 2010 [34] | 32 pts with DSM-IV PSP | Double-blind study of lamotrigine (N=16) (dose: 12,5 → 300 mg/day) *vs*. placebo (N=16) as monotherapy × 12 wks. Primary outcome: NE-YBOCS; response: ≥ 35% reduction on the NE-YBOCS; secondary: SPS, CGI, SP-SAS, SDS, HARS. Assessment: BL to EP, 1-wk × 2 wk, 2-wk × 6 wk, and EP after 12 wk | Lamotrigine did not yield significantly greater efficacy than placebo at study end point as assessed by the NE-YBOCS total score. Secondary outcome measures were consistent with the NE-YBOCS total score. Adverse events of mild-to-moderate intensity and transient with lamotrigine; just one patient felt disoriented and discontinued | Lamotrigine was not superior to placebo in treating PSP on any outcome measure |
| Bloch *et al*., 2013 [62] | 35 pts. (8-17yo) with DSM-IV trichotillomania | Double-blind *N*-acetylcysteine → 2400 mg/day within 4 wk (N=16) *vs*. placebo (N=19) × 12 wk; assessment: MGH-HPS,TSC-C,P, CGI, PAERS q 1wk; IMH-TSS, MIST-C, MASC, CDI q 4wk from BL to EP. | No significant improvement of all measures for *N*-acetylcysteine compared with placebo. Both groups showed significant improvement of hair-pulling symptoms over time. *N*-acetylcysteine-placebo: nausea 30%-63%; diarrhoea 5%-5%; fatigue 0%-11%; insomnia 0%-5%; rash 5%-0%; depression 5%-0%; difficulty swallowing 10%-5% | *N*-acetylcysteine showed no benefits for the treatment of paediatric trichotillomania |
| Grant *et al*., 2014 [94] | 51 pts. with DSM-IV trichotillomania | Double-blind naltrexone 50 mg/day → 150 mg/day over 4 wk (N=25) *vs*. placebo (N=26) × 8 wk; assessment at BL and EP (primary outcome: MGH-HPS; secondary: NIMH-TSS, HARS, HDRS, SDS, CGIs, QoLI) | No significant improvement of all measures for naltrexone compared with placebo. Mild side effects not differing between naltrexone and placebo; only sedation more frequent with naltrexone | Naltrexone cannot be indicated as treatment for trichotillomania |
| Grant *et al*., 2016 [63] | 53 pts. with DSM-5 excoriation disorder | Double-blind *N*-acetylcysteine 1200 mg/day → 3000 mg/day over 6 wk (N=32) *vs*. placebo (N=21) × 12 wk; assessment (primary outcome: NE-Y-BOCS; secondary: SP-SAS, CGIi, SDS, QoLI) at BL q 3wk to EP | Significant treatment type-by-time interactions for the NE-YBOCS total, NE-YBOCS urge/thought subscale, and CGIs. Significant improvement of CGIi, CGIs, NE-YBOCS total and subscales for *N*-acetylcysteine group compared with placebo. No difference between groups on SDS and QoL. Adverse events *N*-acetylcysteine-placebo: nausea 14%-3%; dry mouth 3%-0%; constipation 6%-0%; and dizziness 3%-0% | Some effectiveness of *N*-acetylcysteine in the treatment of SPD, especially for symptoms of urges and craving to pick |
| Leppink *et al*., 2017 [80] | 31 pts. with DSM-5 trichotillomania | Double-blind add-on or monotherapy inositol 6 g/day → 18 g/day over 3 wk (N=19) *vs*. placebo (N=12) × 10 wk; assessment (primary outcome: MGH-HPS; secondary: NIMH-TSS, HARS, HDRS, SDS, CGIi) at BL q 2 wk to EP | No significant treatment type×time interactions for all measures. No difference between inositol and placebo on CGIi. Adverse events with inositol: nausea/gastric discomfort 21.0%; stomach pain 10.5%; headache 10.5%; diarrhoea 10.5%; flatulence 5.3%; ectopic pregnancy 5.3% | Inositol cannot be recommended as first-line treatment of trichotillomania |

**Abbreviations:** BL, baseline; CDI, Children's Depression Inventory; CGI, Clinical Global Impressions scale; CGIi, CGI-Improvement; CGIs, Clinical Global Impressions-Severity; CPS, Clinical Progress Scale; EP, endpoint; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; MASC, Multidimensional Anxiety Scale for Children; MIST-C Milwaukee Inventory for Styles of Trichotillomania–Child; mmd, mean maximum dose; NBIS, Nail Biting Impairment Scale; NBSS, Nail Biting Severity Scale; NE-YBOCS, Yale-Brown Obsessive Compulsive Scale modified for Neurotic Excoriation; PAERS, Pediatric Adverse Events Rating Scale; PITS, Psychiatric Institute Trichotillomania Scale; PSP, Pathological Skin Picking; q, quod; SDS: Sheehan Disability Scale; SPS, Skin Picking Scale; SP-SAS, Skin Picking Symptom Assessment Scale; TIS, Trichotillomania-Impairment Scale; TSC-C, P Trichotillomania Scale for Children–Child and Parent versions; TSS, Trichotillomania-Severity Scale; wk, week(s).

Both drugs were titrated to the maximum dose tolerated and then tapered-off after the switch, while the other drug was being up-titrated. Clomipramine proved to be clearly superior to desipramine in the short-term treatment of TTM.

A third study evaluated the efficacy of clomipramine in a sample of 14 patients suffering from a severe form of onychophagia with no history of OCD. This 10-week crossover study was again performed after a two-week single-blind placebo phase, followed by two consecutive 5 week periods of treatment with either clomipramine (mean dose = 120 mg/day) or desipramine (dose average = 135 mg/day). Again this study showed a clear superiority of clomipramine to desipramine in reducing onychophagia [17]. However, for both these studies, possible carry-over effects could**.**

Selective serotonin reuptake inhibitors (SSRIs) are the most widely used treatment for both children and adults with TTM, despite evidence that their efficacy is no greater than placebo [18]. Although several investigators have suggested

a relation between TTM and OCD [19, 20], which would imply potentially similar responses to serotonin reuptake blockers, others have thought that TTM is best considered a habit [21]. Since fluoxetine has antidepressant effects, the state of the mood of study participants is considered to represent an important variable [22]. Two double-blind crossover studies have apparently shown its poor efficacy in the treatment of TTM. The first of these studies [22], which lasted 18 weeks (6 weeks of administration for each drug interspersed with 5 weeks of wash-out) was performed in a crossover with placebo on 14 patients, all but one women. They all received DSM-III-R diagnosis of TTM, and at the end of the study did not show substantial differences between fluoxetine and placebo for various symptomatological variables, *i.e*., frequency of weekly hair pulling, evaluation of the impulse to tear their hair, number of episodes per week, and estimated total amount of hair lost during the week.

The other study [23] was conducted with similar modalities but lasted 31 weeks (two weeks of placebo administration to both groups and 12 weeks of treatment interspersed with another 5 weeks of wash-out), compared 16 patients (2 of which men) without showing any significant benefit with fluoxetine compared to placebo. On the whole, fluoxetine did not show evidence of efficacy in TTM.

### 3.2. Lamotrigine

The rationale for the use of lamotrigine was two-fold. First, glutamatergic dysfunction has been implicated in the pathophysiology of OCD, [24, 25] a disorder with some phenomenological and possible neurobiological links to pathological (PSP) skin-picking disorder (*e.g*., both PSP and OCD have similar ages of onset, individuals with both disorders spend excessive amount of time engaged in behaviours that are intended to reduce tension or anxiety, rates of co-occurring OCD are elevated in PSP samples and *vice versa*, and PSP is more common in first-degree relatives of OCD patients compared with controls [26, 27]) and second, clinical reports supported the possible efficacy of glutamatergic modulators in the treatment of both impulse control disorders and OCD [28-30]. Lamotrigine is thought to act *via* inactivation of voltage-sensitive $Na^+$ and, possibly, $Ca^{2+}$ channels, leading to suppression of abnormally increased neuronal firing and thus preventing excessive release of glutamate [31, 32]. As lamotrigine may target the medial prefrontal glutamatergic drive to the nucleus accumbens [33], it may correct the underlying pathophysiology and symptoms of PSP.

In a double-blind study, lasting 12 weeks, comparing the efficacy of lamotrigine (up to 300 mg/day) with placebo in 32 patients diagnosed with PSP, the drug showed no superiority over placebo in the treatment of the disorder [34].

### 3.3. Olanzapine

OCD and TTM display significant symptomatological and pathophysiological differences, but also some remarkable similarities [35, 36]. Studies comparing OCD with TTM found the age at onset to be lower for the latter and the gender distribution to differ, in that it is evenly distributed in OCD [37], while women are more affected by TTM than men [38]. Furthermore, OCD patients scored higher on the interference item of the Y-BOCS than patients with TTM on the same item on the Y-BOCSTM and more anxiety-depressive comorbidity than patients with TTM [39]. Differently, from OCD, hair pulling in TTM is only seldom a response to obsessive thoughts [40], but rather a stereotyped behaviour of which the patient is often unaware, much like tics in Tourette's syndrome. Similarly to comorbid OCD and tics, the aura of motor behaviour in TTM is sensory rather than cognitive. Hence, TTM may be likened more to impulsive rather than compulsive OCD [41]. The mediation of both impulse dyscontrol and OCD symptoms by the serotonergic system is strongly supported by literature [42]. Antipsychotic drugs showed some effectiveness in the treatment of OCD if administered as adjunctive agents, but none if given alone [43]. In contrast, tic disorders and Tourette's disorder are unresponsive to serotonin reuptake inhibitors, but responsive to antipsychotic drugs [44]. Hair pulling behaviour in TTM shares features with tic disorders. The neurobiological data point to TTM being a separate, non-OCD repetitive behaviour disorder rather than a subtype of OCD that shares some characteristics with habit and stereotyped movement disorders [40,45-51]. Altered connectivity in striatal pathways is long considered to underlie OCD, and it has been theorised that also in OCD spectrum disorders, like TTM, disruptions in striatal circuitry functioning could be associated with unwanted repetitive behaviours [51]. Treating TTM with drugs usually employed in OCD treatment, *i.e*., serotonin transporter blockers, proved largely unsuccessful. Considering such drugs are also ineffective in Tourette's syndrome and that, based on clinical symptomatology, TTM may be more keen to Tourette's disorder rather than OCD, we might consider drugs usually employed in Tourette's disorder to treat TTM. Antidopaminergic agents (*i.e*., newer antipsychotic or classical neuroleptic drugs) are the first-line treatments for Tourette's disorder [52]. Olanzapine, given its receptor binding profile of $D_2$ receptor block and 5-$HT_{2A}$ blockade, is held to be an "atypical" (*i.e*., expensive) antipsychotic. It also modulates the activity of other dopaminergic ($D_1$ and $D_4$), serotonergic (5-$HT_{1A}$, 5-$HT_7$), histamine ($H_1$), and muscarinic ($M_1$ and $M_5$) receptors, among others.

Its potential utility in TTM treatment has been assessed in a 12-week double-blind study in 2010, which included 25 patients (13 taking Olanzapine at an average dose of 10.8 mg/day *vs*. 12 patients receiving a placebo). All patients had been diagnosed with TTM according to the DSM-IV criteria. In this study, the efficacy and safety of the drug were demonstrated, both in improving the quality of life and in reducing hair-pulling [53].

### 3.4. *N*-acetylcysteine

The glutamate modulator and antioxidant *N*-Acetylcysteine (NAC) is a naturally occurring amino acid. It is available as an over-the-counter supplement. Its use has been widely recognised in the treatment of paracetamol intoxication and as a bronchial liquefier; it has also been experimented with increasing evidence and effectiveness for the treatment of multiple neurological and psychiatric disorders. Although its exact mechanism of action is still unknown, it may act attenuating pathophysiological processes associated with many

CNS disorders, including oxidative stress, apoptosis, mitochondrial dysfunction, neuroinflammation and glutamate and dopamine dysregulation [54]. It is thought to modulate glutamate due to its conversion to cysteine; the latter is a substrate for the glial cell glutamate/cystine antiporter. Cystine uptake by glia induces the release of glutamate from glia into the extrasynaptic space; there glutamate appears to stimulate inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals, ultimately resulting in synaptic glutamate release reduction [55]. NAC showed to possess antioxidant properties [56, 57]. Specifically, NAC provides cysteine, the rate-limiting substrate in the synthesis of glutathione, which is the most important brain antioxidant [58]. Randomised, double-blind, placebo-controlled studies showed NAC to be effective in the treatment of bipolar depression, schizophrenia, substance use disorders and, possibly, of repetitive behaviours in the context of autism spectrum disorders [59-61].

NAC has been tested in several trials conducted on various impulse control disorders, including TTM, skin picking, and nail-biting. These studies have shown conflicting results.

A double-blind RCT, published in 2009, involved 50 patients diagnosed with DSM-IV TTM [62]. 25 patients were administered *N*-acetylcysteine (1200 mg/day for the first 6 weeks, 2400 mg/day for the subsequent 6 weeks), showing a significant improvement in symptoms compared to placebo, with good safety and tolerability [30].

The efficacy of *N*-Acetylcysteine in DSM-IV TTM was also evaluated in 35 paediatric patients aged 8 to 17 years [62]. In this double-blind RCT, 16 patients took *N*-Acetylcysteine for 12 weeks; they did not show a significant improvement compared to the 19 patients who received placebo (in both groups a symptoms improvement was observed over time).

A recent double-blind RCT investigated the efficacy of N-acetylcysteine in excoriation disorder [63]. *N*-acetylcysteine (dose range 1200-3000 mg/day) or placebo were administered for 12 weeks to 66 participants. Compared with placebo, *N*-acetylcysteine treatment was associated with significant improvement in symptoms in about half of the sample, compared to one-fifth of the sample receiving placebo; however, the two samples did not differ for their psychosocial outcome measures [63].

### 3.5. Inositol

Inositol is a constituent of the intracellular phosphatidylinositol second messenger system, which is linked to various neurotransmitter receptors, such as serotonin, dopamine, and glutamate [64-66]. Some clinical trials using add-on inositol in doses ranging from 6 to 18 g/day have shown significant improvements in various disorders, including OCD, binge eating disorder and bulimia nervosa, panic disorder/agoraphobia, depression, and post-traumatic stress disorder [67, 68]. Results have been mixed, however, depending on the duration, dosage, and augmentation methods used for each clinical trial [69-71]. Inositol is generally well tolerated, with many studies reporting mild gastrointestinal problems and some reporting no side effects at all [72]. The exact mechanism by which inositol may benefit psychiatric disorders is still unclear. Neuroimaging assessments of brain inositol have shown that patients with depression have reduced levels in the right frontal lobe. It has also been suggested that inositol may mediate specific interactions between G-protein–coupled receptors and their ligands, particularly in the serotonergic pathways, with the possibility that polymorphisms of the 5-$HT_{1D}$ or 5-$HT_{2A}$ receptors may mediate treatment response in certain disorders, such as OCD [73]. Despite differences between OCD and TTM, both disorders are currently classified as obsessive-compulsive related disorders and neurobiological and neurocognitive similarities between them have been suggested [74, 75]. Hence it is possible that inositol may induce improvement of compulsive symptoms similarly in both OCD and hair-pulling, by modulating available inositol in the brain [76-79].

The only study that compared in a double-blind fashion inositol (from 6 to 18 g/day) and placebo in 31 patients diagnosed with DSM-5 TTM for 10 weeks; the study found no differences in symptom reductions between inositol and placebo [80]. In this study, patients were allowed to continue their previous drug treatment, provided they were stable and with unchanged drug dose during the last three months, prior to intake. Most patients were on SSRIs, thus resulting in the sample being composed of patients with add-on therapy and patients on monotherapy; the data were not analysed drug-wise. Other studies using a more rigorous methodology are needed to confirm the inefficacy of inositol in hair-pulling.

### 3.6. Naltrexone

Naltrexone is a drug commonly used in the treatment of substance abuse disorders, for its ability to modulate the reward mechanisms in the limbic system through the manipulation of glutamatergic, serotoninergic, dopaminergic and opioid neurotransmission. Synthesised in 1963 at Endo Laboratories in New York, naltrexone is an uncompetitive opioid antagonist with high affinity for μ-opioid and κ-opioid receptors (and medium affinity for δ-opioid receptors) in the central nervous system [81, 82]. However, it affects μ-δ–opioid interactions [83] and glutamatergic transmission through binding with adenosine receptors [84]. It has shown efficacy for the treatment of opioid addiction disorders [85] and alcohol use disorder [86].

It acts by reducing both the pleasure of alcohol consumption and the craving and euphoria in opioid and alcohol use disorders [85, 86]. Although currently there are no approved treatments for behavioural addictions, naltrexone is also used in the treatment of pathological gambling, kleptomania, TTM and other disorders [87]. TTM seems to share some symptomatological similarities with substance use disorders (SUDs) [88]. Family history data suggest that individuals with TTM are significantly more likely than controls to have first-degree relatives with SUDs [89]. TTM patients also display difficulties with impulse inhibition, measured by the stop signal task (SST), similarly to people with SUDs [90, 91]. Since TTM and SUDs appear to be clinically connected, so it could be that medications effective in one could constitute candidates for the treatment of the other. In fact, the opioid receptor antagonist, naltrexone, a drug used in many SUDs, even in those not involving the opiate use, has previously been studied in the treatment of grooming behaviours

in animals and in human TTM. Opioid antagonists reduced self-licking or self-chewing behaviours in 63% to 91% of dogs with acral lick dermatitis [92, 93].

In a recent double-blind RCT, out of 51 patients diagnosed with TTM, 25 were administered naltrexone (up to 150 mg/day) and 26 placeboes; the study found no statistically significant difference between the naltrexone and the placebo group [94]. The authors concluded that naltrexone cannot be used as a viable TTM treatment.

We summarized the main results of our study in Table **1**.

From our literature review we have found that, to date, there is no single line in the treatment of TTM, excoriation disorder and nail-biting. With regard to antidepressant drugs, the literature data show a good efficacy of clomipramine, although the studies supporting this are quite old and dated [14-16]; differently, fluoxetine has not shown particular utility in reducing symptoms [22, 23]. The atypical antipsychotic olanzapine, although evaluated in a single study, has proved to be quite effective in TTM, perhaps because this disorder can be considered more similar to Tourette's syndrome than to OCD [53]. Likewise, in different studies, *N*-acetylcysteine [62, 63] proved to be efficacious in treating these disorders. In contrast, lamotrigine, inositol and naltrexone failed to provide any evidence of benefit, hence they can hardly be proposed as possible treatments [34, 80, 94]. Despite this, further studies will be necessary to evaluate the real effectiveness of those pharmacological treatments (clomipramine and olanzapine) which, apparently, have proved useful in reducing the symptomatology of TTM, excoriation disorder and nail-biting. Furthermore, other possibly useful substances, like methylphenidate and atomoxetine, that were shown to be both useful in few patients with comorbid attention-deficit/hyperactivity disorder (ADHD) and skin picking [95] or TTM, respectively [96], as well as to be associated with the onset of skin picking [97] or with TTM [98], will have to be carefully assessed in rigorous trials. We hate concluding "further studies are needed to address whether…", but in this case, it is highly appropriate.

Summarising, the quality of the first studies was methodologically quite poor, while all studies are underpowered. The small sample size is likely to affect RCTs of TTM and excoriation disorder for the years to come. On the other hand, all studies have a low risk of bias; most notably, there was minimal financial involvement of drug manufacturers (just two papers) and few authors were industry affiliated in the included papers (just one). Most authors are highly esteemed by colleagues for their intellectual honesty. Our reviews limitations and strengths reflect those of the included studies.

## CONCLUSION

Considering collectively all gathered data, the treatment of TTM, excoriation disorder and nail-biting is still rather disappointing. Conjectures made from preclinical studies and the relative pathophysiological hypotheses found poor confirmations at a clinical level. The impossibility to draw firm conclusions is also to be attributed to the generally poor quality of clinical studies, that spanned across a 28-year interval, with some big leaps from one study to the other (Table **1**), during which many changes in the attitudes towards clinical studies took place. There is a need for further studies on medication with some effect on OCD spectrum disorders such as risperidone or aripiprazole [99, 100], preferably using a therapeutic drug monitoring approach [101, 102], and the integration of pharmacological trials with non-pharmacological, such as TMS [103, 104], and psychotherapeutic interventions to achieve some improvement in some patients. Our results point to the need for integrating personalised medicine principles in the treatment of this group of disorders.

## CONSENT FOR PUBLICATION

Not applicable.

## STANDARD OF REPORTING

PRISMA guidelines and methodology were followed.

## FINANCIAL AND COMPETING INTERESTS DISCLOSURE

This work has not been supported by any funding. All authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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