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Anxiety, Obsessive Compulsive and Related Disorders (B Brennan and D Dougherty, Section Editors)

# Review of Psychotherapeutic Approaches for OCD and Related Disorders

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#### **Opinion statement**

Obsessive-compulsive disorder (OCD) can take many forms, limited only by the imagination of the human mind. Advances in research surrounding OCD have established that efficacious treatments, such as exposure and response prevention (ERP), do exist. Even though ERP should provide the foundation for OCD treatment, ERP can be perceived as a highly aversive treatment, as evidenced by high drop-out and relapse rates (Abramowitz, Can J Psychiatr 51:407-416, 2006). As a result, research has started to examine other empirically supported strategies that may improve treatment outcome and reduce risk of future relapse. Building upon the foundations of ERP, these strategies may lead to more personalized treatment programs, particularly for complex or difficult-to-treat cases. Specifically, emerging research regarding the role of inhibitory learning in exposure therapy may be an important area in which to enhance the robustness of treatment gains. Further, advancements in technology have provided new pathways to disseminate personalized and targeted treatments, particularly for individuals who lack access to inperson treatment. In light of these exciting new ways to conceptualize, implement, and disseminate empirically based treatments, continued focus on bridging the gap between emerging science and clinical practice is necessary as the landscape of OCD treatment changes.

#### Introduction

Obsessive-compulsive disorder (OCD) is an insidious disorder that can take many forms, resulting in high levels of impairment, as evidenced by the World Health Organization identifying OCD as one of the top ten most disabling disorders [1]. OCD is characterized by intrusive and unwanted thoughts, images, or impulses that provoke anxiety (i.e., obsessions), as well as behavioral and mental efforts aimed at neutralizing that anxiety (i.e., compulsions). OCD is a notably heterogeneous disorder, and recent research has determined four symptom dimensions of OCD: (1) concerns about germs and contamination; (2) being responsible for harm, injury, or bad luck; (3) unacceptable thoughts; and (4) symmetry, completeness, and the need for things to be "just right" [2]. As interest in understanding this heterogeneous disorder has increased, we have observed significant advances in research focusing on treatment outcome.

Further, with the release of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, there has been increased attention surrounding the newly formed obsessive-compulsive and related disorders (OCRDs) chapter. This diagnostic class is characterized by obsessive thinking and/or repetitive behaviors, encompassing OCD, body dysmorphic disorder (BDD), hoarding disorder (HD), trichotillomania (TTM), and skin picking (or excoriation) disorder (SPD). As a result, more recent research has focused on the similarities and differences among these disorders, especially with regard to treatment strategies.

## Cognitive behavioral therapy

According to contemporary cognitive models of OCD [3], intrusive thoughts are a normal experience in clinical and non-clinical populations, and the difference between normal intrusions and clinical obsessions is one's interpretation or appraisal of those thoughts. For example, individuals with OCD often believe they are responsible for their thoughts and regard their thoughts as being overly important. These maladaptive beliefs, coupled with the experience of intrusive thoughts, lead to increased anxiety and a consequential urge to engage in compulsions to reduce that anxiety. However, compulsions negatively reinforce the anxiety and obsessive belief, thereby maintaining the OCD cycle. Therefore, cognitive behavioral therapy (CBT) focuses on breaking this cycle by targeting the maladaptive thoughts, emotions, and behaviors that contribute to the onset and exacerbation of symptoms in order to promote new learning and behavior change.

#### **Exposure and response prevention**

The core treatment strategy in CBT for OCD is the use and practice of exposure and response prevention (ERP). ERP as a front-line treatment for OCD has been repeatedly demonstrated both within clinical research and naturalistic settings [4, 5]. Based on the learning theory and the habituation model, ERP asks individuals to be "exposed" to the stimuli that cause fear and anxiety and to consequently "prevent a response" that would otherwise neutralize their anxiety and reinforce their obsessive thoughts. The goal of exposure therapy is to teach clients that anxiety is fleeting and that they will habituate to the fear with repeated and prolonged exposure. According to Abramowitz [4], ERP is thought

to reduce OCD symptoms by extinguishing the conditioned response to feared stimuli, correcting dysfunctional beliefs that maintain obsessive fears, and enhancing self-efficacy. Meta-analytic findings have demonstrated that ERP results in large effects (d=1.41) [6] and OCD symptom reduction around 60 % [4, 5, 7].

## Inhibitory learning theory

More recent evolutions in our understanding of the exposure process have focused on the role of inhibitory learning as a mechanism of change and possible avenue for enhancing treatment outcomes [8••]. Craske et al. [9] outlined how inhibitory learning mechanisms may be central to the extinction process, with exposure promoting new learning about the feared stimuli and expected outcome. This new learning is not thought to replace the previous associations but, instead, competes with the initial, excitatory learning that sustained the fear. Based on their integration of the extinction literature, the authors suggested these new inhibitory associations can be created independent of the amount of change in fear levels, which is in contrast with habituation-based models. Within this framework, the use of post-exposure cognitive therapy strategies were encouraged to promote further learning that maximally violates client's pre-exposure expectancies [8••].

In an effort to translate basic research into clinical application, Craske and colleagues [8••] outlined eight therapeutic strategies for enhancing inhibitory learning (see Table 1). While specific evaluation of inhibitory learning mechanisms within OCD has been limited, initial evaluation is supportive of the efficacy of inhibitory learning as a mechanism of extinction. For example, Kircanski et al. [10] demonstrated the use of variable or random exposures (aimed at enhancing inhibitory learning), which produced similar reductions in non-clinical contamination fears as standard hierarchy-based exposures. While targeted research is necessary with clinical OCD populations, the inhibitory learning literature demonstrates significant advances in implementing basic learning and memory research into the clinical domain.

## Cognitive therapy for OCD

An important component of treatment for OCRDs is cognitive therapy (CT), as maladaptive beliefs and interpretations are hypothesized to be at the core of OCD. CT has been found to be effective in reducing OCD symptoms and treatment drop-out rates [11–13].

Wilhelm and Stekeee [14] developed a protocol of CT for OCD, which focuses on modifying maladaptive beliefs in order to reduce symptoms. Of note, there is little emphasis on engaging in exposure therapy given that CT focuses more on modifying the underlying cognitive beliefs than the associated behavioral components. An open trial of CT for OCD demonstrated that 24 weeks of CT resulted in reductions in OCD symptom severity, depressive symptoms, and dysfunctional beliefs for individuals with OCD, when

#### Table 1. Therapeutic methods for enhancing inhibitory learning in exposure therapy

Expectancy violation	Goal: develop significant mismatch between client expectancies and exposure outcome.
	Key points:
Deepened extinction	<ul> <li>Clearly identify the client's expectancies of the adverse outcome and target those specific criteria in the exposure.</li> <li>Utilize cognitive strategies after, rather than before, the exposure to enhance inhibitory learning. Use of strategies before exposure may reduce client expectancy of the outcome, thereby interfering with learning.</li> <li>Goal: enhance inhibitory learning and reduce spontaneous recovery of client's fear.</li> </ul>
·	Key points:
Occasional reinforced extinction	<ul> <li>Combine multiple fear triggers into one exposure.</li> <li>Exposure to one or both of the triggers should be completed prior to integration.</li> <li>Both triggers should be related to the same expected feared outcome.</li> <li>Goal: reduce reacquisition of fear when faced with negative/feared outcomes.</li> </ul>
	Key points:
	<ul> <li>Occasionally seek out negative outcomes during or following exposures as this may facilitate additional learning.</li> </ul>
Removal of safety signals	Goal: eliminate safety behaviors/signals that may interfere with inhibitory learning.
	Key points:
Variability	<ul> <li>Even subtle safety behaviors/signals may reduce the expectation of the feared outcome, thereby reducing the degree of expectancy violation.</li> <li>Goal: enhance retrieval of inhibitory associations by creating more retrieval cues, thus reducing context-based resurgence of fear.</li> </ul>
	Key points:
Multiple contexts	<ul> <li>Variability may take the form of triggering stimuli, fear level, and timing between exposures.</li> <li>Using these methods promises promotion of relapse prevention by better capturing the variability of post-treatment life.</li> <li>Goal: reduce context-dependent nature of exposure learning to reduce</li> </ul>
	re-emergence of targeted fears.
	Key points:
	<ul> <li>Complete exposure exercises in different settings.</li> <li>Consider using different environments, individuals, and time of the day/week.</li> </ul>
Reconsolidation	Goal: capitalize on the process of re-encoding of previous memories following retrieval to weaken fear-based memories.
	Key points:
	<ul> <li>Evidence for this technique is still in preliminary stages.</li> <li>Brief exposure to feared stimuli in advance of a prolonged exposure may weaken the original memory trace.</li> </ul>
Summary of therapeutic strategies for enhancing exposure through inhibitory learning is presented in [8••]	

compared to a waitlist control [15]. Recently, Wilhelm and colleagues [16•] examined mechanisms of change in CT for OCD and found that beliefs about perfectionism and certainty, as well as schemas related to dependency and incompetence, mediated changes in OCD symptom severity, suggesting that these factors contribute to overall symptom reduction in CT.

## Cognitive bias modification

Another cognitive approach is cognitive bias modification (CBM), which targets mechanisms of attention, interpretation, and/or memory that have been implicated in the maintenance of psychological disorders. CBM programs targeting interpretation bias (CBM-I) have been shown to reduce negative OC beliefs, corresponding to decreases in distress and urges to neutralize during OC stressor tasks [17, 18]. Additionally, Salemink, Wolters, and de Haan [19•] found CBM-I to be a valuable augmenter of ERP treatment in adolescent OCD clients, reducing symptom severity based on clinician and client report.

In a recent study, Amir, Kuckertz, Najmi, and Conley [20] integrated CBMs for attention, attentional control, interpretation, and working memory with ERP for OCD clients. Participants were asked to create their own stimuli in order to build a hierarchy of self-directed ERPs and were encouraged to complete these exposures on their own during the study. Results showed that participants experienced benefits that were on par with studies of clinician-administered ERP. Furthermore, CBMs that induced positive interpretation bias and improved attentional control were particularly effective in reducing OCD symptom severity and functional impairment. Overall, preliminary research suggests that as an adjunct to ERP, CBM-I holds promise for the future in that it is portable, economical, and suited to personalization.

## Couple-based cognitive behavior therapy

Though CBT is often conducted on an individual basis, it is important to consider the role of family in the maintenance of OCD symptoms. Family accommodation, in which family members and significant others accommodate OCD-driven behavior by helping or allowing the individual to engage in rituals, can be detrimental to treatment progress [21]. Family accommodation is positively associated with symptom severity and negatively associated with treatment outcome, which reinforces the importance of including family members in treatment [22]. Thus, Abramowitz et al. [23] developed a couple-based CBT program for individuals with OCD. Pilot data demonstrated a reduction in OCD symptom severity and family accommodation from pre- to post-treatment, with gains maintained at 1 year follow-up. However, though relationship satisfaction and constructive communication improved across treatment, both factors returned to baseline at 6 months follow-up. This study supports the importance of family factors in the maintenance and treatment of OCD, though more research is needed to improve long-term outcomes.

## Acceptance and commitment therapy

A new "wave" of CBT gaining significant empirical support in the last 10 years is acceptance and commitment therapy (ACT), which uses acceptance and mindfulness-based skills to increase psychological flexibility. ACT focuses on six core processes that target psychological flexibility: acceptance, cognitive fusion, present moment awareness, self as context, values, and committed action [24].

The basis for ACT lies in contextual behavioral science, in which emphasis is placed on the context and function of internal experiences, rather than the content and frequency with which they occur. Therefore, individuals learn to recontextualize maladaptive thoughts, feelings, and sensations in order to promote new learning and behavior change. Though ACT has a distinct theoretical approach, it is nonetheless a behavioral treatment [25]. Therefore, ACT for OCRDs and other anxiety disorders encompasses exposure therapy, but confronting stimuli is seen as an exercise that builds psychological flexibility and willingness to experience obsessions and anxiety, rather than habituation [26]. For example, ACT-enhanced exposure therapy for an individual with intrusive thoughts might consist of the individual saying the intrusive thoughts with a funny voice or in a song to demonstrate thoughts are just thoughts, thereby practicing defusion [26].

A recent meta-analysis found psychological flexibility was significantly correlated with OCD symptoms, along with generally modest support for the use of ACT in OCD [27•]. Additionally, effect sizes for ACT interventions for anxiety and OC-spectrum disorders were comparable to effect sizes for CBT and other manualized treatments, suggesting that ACT may be a strong alternative to other treatments.

## Motivational interviewing

Since its inception, the use of motivational interviewing (MI) has continued to evolve from substance use to other domains of psychopathology, including anxiety disorders [28]. However, MI's use in OCD is still in its infancy, with the majority of studies limited by sample size. MI has not evidenced significant impact on OCD symptoms as a stand-alone treatment [29], although preliminary findings suggest MI can be effectively integrated into ERP while maintaining integrity of the treatment [30]. While early studies suggest MI may not result in significant increases in treatment readiness, some evidence suggests it may be beneficial for increasing treatment engagement, even with those identified as treatment refractory [29]. Additionally, Meyer and colleagues [31] reinforced these findings, demonstrating an integration of MI with CT strategies prior to group-based CBT for OCD resulted in greater symptom reduction than groupbased CBT alone, which the authors suggested may be due to greater homework compliance. MI was also associated with greater speed of symptom reduction in a study of pediatric OCD [32]. In summary, variable evidence exists for the role of MI within OCD treatment, and as stated by Simpson and colleagues [33], the best method and dosage for administering MI within OCD is still unclear.

Of note, OCD therapists are often wary of giving too much time to discussion and discovery of motivations in treatment, as overanalyzing is a hallmark symptom of OCD that promotes inaction. For this reason, combining the MI approach within the context of ERP may be especially challenging. Accordingly, MI may be most useful as part of a pre-treatment program, preparing individuals for ERP through integration with other treatment readiness techniques.

#### **Body dysmorphic disorder**

BDD is characterized by preoccupations with a perceived physical defect that results in compulsive behavior, such as checking the mirror or trying to conceal

the perceived flaw. Wilhelm, Phillips, and Steketee [34] proposed that individuals with BDD exhibit interpretation and attentional biases, such that they selectively attend to perceived defects and give undue importance to negative thoughts about body image. These biases cause anxiety and shame, which results in significant avoidant and ritualistic behavior and confirms the initial preoccupation. Thus, CBT for BDD primarily consists of ERP and perceptual retraining. ERP for BDD targets the behaviors that maintain the preoccupation about one's body part(s) and associated distress, such as seeking reassurance, checking oneself in the mirror, and comparing oneself to others. For example, an individual with preoccupations about one's nose might continually check his/her nose in the mirror or ask friends if they think his/her nose looks deformed. Exposure for this individual might consist of resisting urges to ask others or check mirrors.

Given the association between BDD and cognitive biases, treatment for BDD also often incorporates perceptual retraining, in which individuals objectively talk about their body parts without judgment in an effort to practice viewing oneself in a neutral manner, thereby resisting urges to scrutinize [34]. For example, rather than focusing on the thought "my nose is ugly," one might practice looking in the mirror and observing other parts of his/her body, such as "my hair is brown and my shirt is purple." Another potential treatment strategy for BDD is MI, as BDD is associated with poor insight [35•]; however, research is needed in order to provide empirical support for this hypothesis.

Overall, research regarding treatment for BDD has been relatively limited; there have been only three studies to date that have compared CBT to a waitlist control condition [36–38]. A recent study showed that CBT was more effective than anxiety management (e.g., practicing muscle relaxation and deep breathing) in treating BDD [39], and these gains were maintained after 1 month, though both treatments resulted in symptom reduction. More research is sorely needed with larger sample sizes, longer follow-up periods, and particularly more information regarding the mechanisms of change, as this is still relatively unknown.

# **Hoarding disorder**

HD is characterized by having difficulty discarding possessions, regardless of the value of the possessions, which results in significant clutter in one's living space. Frost and Hartl [40] proposed a cognitive behavioral model of HD, in which dysfunctional beliefs about possessions and information-processing deficits lead to excessive saving behavior in an effort to avoid anxiety that could be caused by discarding a potentially necessary item. Specifically, individuals with HD tend to view their possessions as being overly important, valuable, and necessary, and exhibit difficulties in decision making and organization.

CBT for HD primarily consists of ERP and skills training. ERP for HD targets fears of discarding and/or not acquiring an item that might be important or needed in the future. Therefore, individuals with HD practice engaging in more discarding and less acquiring, thereby reducing the amount of clutter in one's home [41]. In addition to ERP, treatment for HD consists of skills training to target cognitive difficulties, such as decision making and organization, that likely impede on one's ability to cope with clutter [41]. For example, an individual with HD might have difficulty discarding possessions due to their

perceived sentimental value of all possessions. Therefore, treatment might consist of practicing making decisions about discarding possessions, while also working to organize one's belongings. Though treatment for HD involves ERP, it is mostly focused on skills training to target cognitive deficits, using ERP as a means by which to practice these skills.

A recent meta-analysis of 12 studies regarding treatment for HD showed that CBT generally results in symptom reduction, with effect sizes of 0.82 (g) [ $42^{\bullet}$ ]. More specifically, there were large effects only in decreases in difficulty discarding (g=0.89) and moderate effects on clutter, acquiring behaviors, and functional impairment (g's=0.70, 0.72, 0.52, respectively). This suggests that though overall symptom severity and difficulties in discarding decrease in treatment, clients are still significantly impaired in their ability to function in everyday life, which may be due to the significant amount of clutter that still exists in their home.

Additionally, in a treatment study targeted at hoarding in a geriatric population, Ayers and colleagues [43] combined cognitive rehabilitation techniques with behavior therapy. Results showed that overall symptom severity was significantly reduced with large effect sizes after the intervention, and clutter was reduced with medium effects. However, generalizability of the findings may be limited due to the sample size (N=11) and lack of follow-up data.

Taken together, though research regarding the treatment of HD is still nascent, future research should focus on developing interventions to target clutter, as this appears to be a harder-to-treat symptom of HD.

## Trichotillomania and skin picking disorder

TTM is characterized by recurrent pulling of hair from parts of one's body, such as the scalp, eyebrows, or eyelashes. SPD is characterized by recurrent picking, rubbing, scratching, or digging into one's skin in an attempt to remove perceived imperfections. Behavioral models of TTM and SPD suggest that individuals engage in these behaviors to alleviate distress or anxiety, which generates a reinforcement cycle and maintains the problematic behaviors. TTM and SPD are broadly considered to be body-focused repetitive behaviors (BFRBs) and, therefore, have similar treatments.

CBT for TTM and SPD primarily consists of habit reversal training (HRT), which is a behavioral treatment for BFRBs. HRT focuses on building awareness about the frequency of and triggers for BFRBs (i.e., awareness training), as well as practicing a behavior that directly competes with the BFRBs (i.e., competing response training). A common competing response is putting one's hands in fists when one feels an urge to pull or pick.

A meta-analysis of seven treatment trials of TTM [44] showed that there was a large effect of behavior therapy when compared to control conditions, supporting the use of HRT in the treatment of TTM. However, relapse rates remain high, suggesting the need for more research regarding the underlying mechanisms of TTM in order to inform augmentative strategies to enhance treatment.

One such mechanism that has been hypothesized as integral in the maintenance of TTM is experiential avoidance [45]. Woods, Wetterneck, and Flessner [46] integrated acceptance-based principles into HRT for TTM, and results indicated that treatment gains were maintained at 3 months follow-up.

Further, reductions in experiential avoidance were associated with reductions in pulling symptoms.

Another mechanism that has been largely studied in this area is emotion regulation, as it has been hypothesized that difficulties regulating affect may be at the core of BFRBs [47]. To target these difficulties, Keuthen and colleagues [48•] evaluated the use of dialectical behavior therapy (DBT) with CBT in treating TTM in a randomized controlled trial that compared the augmentative use of DBT with an active control condition. DBT is a skills-based treatment often used for individuals with affective dysregulation, in which individuals are taught mindfulness, distress tolerance, interpersonal effectiveness, and emotion regulation in order to promote behavior change. Results showed that participants demonstrated significant improvements in overall symptom severity, emotion regulation, experiential avoidance, and mood and anxiety from pre- to post-treatment, and these results were mostly maintained at 6 months follow-up.

Research regarding the treatment of TTM and SPD has been relatively limited, but preliminary studies have suggested that HRT is an effective treatment but may be better implemented when combined with emotion-focused treatments, such as DBT. Nonetheless, replications and extensions of previous studies are needed in order to strengthen the empirical support for the treatment of these conditions.

# The use of technology in treatment

It has been estimated that the average time between receiving a diagnosis of OCD and finding appropriate treatment is 7 years [49]. There are often geographical and financial barriers that limit client access to in-person treatment. However, as the internet has become more widely available, it has opened new avenues for treatment delivery.

The pioneers of computer-assisted therapy for OCD were developing treatments during the early days of personal computing [50]. The oldest and best known program, *BT Steps*, is a computerized telephone system, in which clients call to learn about OCD, discuss their symptoms and rituals, set goals, and design ERPs. BT Steps has been the subject of two studies that have demonstrated its acceptability and effectiveness as being on par with clinician-guided ERP [51, 52].

A few studies have found support for internet-based CBT programs consisting of manualized treatments that require minimal contact with a therapist [53, 54]. Others have shown that exposure-based CBT conducted via phone [55] and videoconferencing [56] can be as effective as standard ERP conducted in an office. Furthermore, telephone-based CBT was found to be an effective and likeable treatment for adolescent OCD [55]. Additionally, recent studies have evaluated internet-based programs for other OCRDs, such as hoarding [57].

The limited evidence in support of these modalities is promising and is likely to become part of standard care over time. Of note, there are also many applications available for smartphones that are meant to act as stand-alone, self-help OCD treatments and/or as therapy tools in conjunction with regular office visits (e.g., Mayo Clinic Anxiety Coach, Live OCD Free). The development of such apps has outpaced the research on them, although many are based on research relating to CBT and ERP for OCD.

#### Stepped care in OCD

The use of technology has drastically enhanced opportunities for dissemination of efficacious OCD treatments and has opened the possibility of stepped care approaches, especially for those in rural setting or areas where trained OCD therapists are not readily available. At the bottom level, self-directed therapies with minimal therapist contact may be adequate for those with mild or moderate OCD symptoms. As discussed by Mataix-Cols and Marks [58] in their review, evidence of the efficacy of these treatments exists, though the dosage of therapist contact necessary to optimize outcomes is unknown; however, even minimal therapist contact may increase motivation and reduce drop-out. The authors suggested these interventions could be managed in a primary care setting, with more severe clients stepping up to the outpatient treatments discussed above. Additionally, evaluation of stepped care approaches in OCD is limited. Preliminary data regarding stepped care programs show promise, such that completers evidenced a 61 % reduction in Y-BOCS scores and the authors suggested the stepped care program may be more cost-effective than traditional outpatient treatment [59].

Building upon the foundation of stepped care, it is important to note that many clients with complex or particularly severe presentations fail to respond to traditional treatment approaches. Therefore, intensive residential treatment (IRT) programs have been developed to provide a greater treatment dose to those who do not respond optimally to lower levels of care. Empirical evaluations of IRT support its efficacy, as evidenced by clients experiencing up to 25 % symptom reduction [60, 61]. These programs utilize a multi-disciplinary approach, primarily within the CBT/ERP framework, augmenting traditional ERP with other treatment approaches, such as those discussed above.

## **Relapse prevention**

While significant strides in our understanding of OCD and exposure therapy have been made over the past two decades, there has been limited independent focus on specific strategies for relapse prevention. One study by Hiss, Foa, and Kozak [62] tested a 4-day, multi-component relapse prevention program that included training in cognitive restructuring, self-directed exposure, goal setting, methods for enhancing social support, and other anxiety management techniques. Results indicated the program related to greater maintenance of gains at 6 months and long-term follow-up, with 75 % of participants maintaining their gains. Based on these findings, future research should target understanding the specific elements that may reduce relapse in OCD.

#### **Conclusions and future directions**

OCD is a notably heterogeneous disorder that can be difficult to treat. Based on extant literature, exposure to feared stimuli and modification of problematic responses (i.e., ritual prevention) remain at the core of any effective, empirically driven treatment for OCD. However, OCD treatment research is experiencing a

renaissance of empirically supported strategies that may effectively augment exposure processes and ritual prevention strategies (e.g., inhibitory learning, ACT). Therefore, as treatment providers, it is important to stay current on emerging research that informs our implementation of exposure therapy and guides decisions related to treatment augmentation.

#### **Compliance with Ethics Guidelines**

#### **Conflict of Interest**

Brittany M. Mathes declares that she has no conflict of interest. Nathaniel Van Kirk declares that he has no conflict of interest. Jason A. Elias declares that he has no conflict of interest.

#### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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