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Pharmacological Interventions as They Relate to Intrusive Thinking

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Abstract

Intrusive thoughts are features of numerous psychiatric disorders. They vary widely in form, duration, frequency, and severity. They are associated with disorders with widely differing pathophysiology, and they are likely to respond to different pharmacological treatments. It is possible that intrusive thoughts represent a cross-diagnostic symptom that can be a pharmacological target in their own right, separate from the associated disorder. This chapter considers the challenges in studying intrusive thoughts as a separate entity. It examines intrusive thoughts that are symptoms of several different psychiatric disorders and reviews the medications that have been used to treat them. It holds that relatively little is known about the effects of psychiatric medications on intrusive thoughts, either within disorders (separate from other symptoms) or across disorders. A wide range of medications is used to treat intrusive thoughts that target different neurotransmitter systems. In addition to the psychopharmacological armamentarium, new, single dose treatments (e.g., ketamine, psilocybin, and MDMA) have emerged that may specifically address intrusive thoughts across the psychiatric spectrum. In conclusion, possible directions are discussed for identifying subcategories of intrusive thoughts that could advance research and treatment in this area.

Introduction

While most of the time we have a sense of control over our own thoughts, sometimes it seems as if our thoughts control us. Under these circumstances, thoughts appear to assert themselves into our consciousness, influencing mood and sometimes behavior. These unwanted images and urges, or "intrusive thoughts," can interfere with everyday functioning (Clark 2005). In an early definition, Rachman (1981) identified three criteria for intrusive thoughts: (a) the thought interrupts ongoing activity, (b) the thought is recognized to be

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of internal origin, and (c) the thought is difficult to control. When intrusive thoughts become severe enough to interfere with normal function, they become clinically significant psychiatric symptoms and thus potential targets for treatment. In this chapter we review several psychiatric disorders in which intrusive thoughts are a prominent symptom and summarize the medications that have been used to treat these disorders. We also comment on future directions of pharmacological treatments for this symptom.

In the context of psychiatric disorders, intrusive thoughts vary widely in their nature, form, frequency, and controllability, and this variance can make them difficult to study as well as to treat. Intrusive thoughts may occur as part of normal human experience, such as in the case of grief or intense romantic love, or they may indicate a serious psychiatric disorder such as psychosis (Table 15.1). They vary in the degree to which they interrupt normal thinking and activity, whether they are perceived to originate from within the individual or from outside, and the extent to which the individual feels they can be controlled. Some intrusive thoughts may be experienced as pervasive emotional experiences, such as worry or rumination in anxiety and depression, whereas others may be experienced as either spontaneous intrusive experiences, such as compulsions in obsessive-compulsive disorder (OCD). Others are elicited by discrete environmental stimuli, such as triggers in posttraumatic stress disorder (PTSD) or craving elicited by cues in drug users. Intrusive thoughts also differ in content along several modalities, including verbal, visual imagery, and sensorimotor phenomena (e.g., urges and compulsions) and the degree to which they can be suppressed or controlled by various behavioral procedures. Although studying these dimensions may shed light on the psychological and neural processes underlying intrusive thoughts, there have been few attempts to categorize intrusive thoughts along any of these dimensions.

An obvious follow-up to recognizing this variability is to ask: To what extent do pharmacological or behavioral treatments depend on the nature of the intrusive thoughts? Certain drugs, for example, may be effective for intrusive thoughts related to depressive rumination and suicidality, whereas others may more effectively target stimulus-elicited urges. Careful examination of intrusive thoughts as separate entities may reveal shared mechanisms across diagnoses, which can be revealed by focusing on medications that are efficacious across disorders. Naltrexone, for example, is used for opioid use as well as for OCD, and aripiprazole is used for suicidal thoughts and for gambling. Such analysis is consistent with the RDoC approach, designed to identify the neurobiological and cellular mechanisms underlying psychopathological states. Increasingly, researchers have focused on the neural features of intrusive thoughts. For example, Popa et al. (2016) report that stimulation in the dorsolateral prefrontal cortex in patients with epilepsy produces the persistent thoughts that often presage frontal seizures. Other studies (e.g., Hellerstedt et al. 2016) have used a Think/No-Think procedure to track neural activity related to unwanted memories using electrophysiological measures. Kühn et

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Table 15.1 Examples of intrusive events that occur in different psychiatric disorders.

Disorder	Symptoms of Intrusive Thinking
OCD	Recurrent and persistent thoughts, urges, or images that are experienced as intrusive or unwanted; cause marked anxiety and distress; individual attempts to reduce or ignore thoughts and urges, or neutralize them with an action
	Compulsions: repetitive behaviors that the individual feels driven to perform
Body dysmorphic disorder	Preoccupation with one or more perceived defects or flaws in physical appearance
Eating disorders (bulimia nervosa, anorexia nervosa)	Intense fear of gaining weight; undue influence of body weight on self-evaluation
Gambling	Preoccupation with gambling, persistent thoughts of reliving past gambling experiences, thinking of ways to get money to gamble; often gambles when distressed
Pyromania	Fascination with, interest in, curiosity about, or attraction to fire; pleasure, gratification, or relief when setting fires
Kleptomania	Recurrent failure to resist impulses to steal objects
Intermittent explosive disorder	Failure to control aggressive impulses (verbal or damage to property)
Major depressive disorder	Rumination on feelings of worthlessness or guilt
Generalized anxiety disorder	Recurrent worries about various dimensions of life, including work, family, romance, or others
PTSD	Recurrent, involuntary, and intrusive distressing memories of a traumatic event; hyperreactivity to cues and reminders of the event; avoidance of reminders of the event
Psychosis	Preoccupation with delusions or false beliefs*
Substance use disorder	Craving, strong desire to use a drug

*Psychosis may be part of many different disorders

al. (2013) used fMRI to show that there was greater activity in brain regions involved in language production in healthy individuals who reported high, compared to low, habitual tendencies for intrusive thought. This focus on intrusive thoughts as entities in their own right provides an opportunity in the future to investigate pharmacological interventions that target such thoughts.

Here we review the main medications that are used for psychiatric disorders for which intrusive thoughts are a major feature (Table 15.2). We separate the medications into categories based on first-line treatment, second-line treatment, and experimental approaches. The medications listed under the first two categories are considered standard care and were drawn from the online clinical decision support resource site UpToDate. The medications listed under experimental approaches were drawn from a review of the literature (PubMed).

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Table 15.2 Drugs used to treat psychiatric disorders with intrusive thoughts in first-line treatment, second-line treatment (where several randomized control trials have shown strong evidence), and experimental approaches (where some small studies may show effects). MAOI (monoamine oxidase inhibitor), MDMA (3,4-methylenedioxymethamphetamine), SNRI (serotonin and norepinephrine reuptake inhibitors), SSRI (selective serotonin reuptake inhibitors), TCA (tricyclic antidepressants).

Disorder	First-Line Treatment	Second-Line Treatment	Experimental Approaches
OCD	SSRIs (all have been FDA approved except citalopram and escitalopram), clomipramine (TCA)	SNRIs (e.g., venlafaxine), augmentation with antipsychotic (e.g., risperidone)	Psilocybin, eszopiclone, substance P, neuropeptide Y, vasopressin, riluzole, ketamine, D-cyclosterine
Body dysmorphic disorder			
	SSRIs (escitalopram or fluoxetine have the most evidence)	Clomipramine	Augmentation with atypical antipsychotics, oxytocin
Eating disorders			
Bulimia nervosa	SSRIs (e.g., fluoxetine)	TCA (e.g., desipramine), trazodone, MAOI (e.g., phenelzine), topiramate	
Anorexia nervosa	Psychotherapy	TCA (e.g., desipramine), trazodone, MAOI (e.g., phenelzine), topiramate	D-cyclosterine plus exposure-based therapy
Gambling	SSRIs	Opioid antagonists	Glutamatergic agents, lithium (for comorbid bipolar disorder), topiramate
Pyromania	None	Mood stabilizers (e.g., lithium, carbamazepine, valproate, SSRIs), opioid antagonists	
Kleptomania	None	SSRIs, opioid antagonists	

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Table 15.2 (continued)

Disorder	First-Line Treatment	Second-Line Treatment	Experimental Approaches
Intermittent explosive disorder	SSRIs	Mood stabilizer, phenytoin, oxcarbazepine, carbamazepine, lamotrigine, valproate, lithium	Atypical antipsychotic (e.g., ziprasidone, clozapine, risperidone, and olanzapine)
Major depressive disorder	SSRIs	SNRIs, serotonin modulator, TCA, MAOI, bupropion, mirtazapine	Ketamine, psilocybin, LSD, opioid medications
Generalized anxiety disorder	SSRIs, SNRIs	Buspirone, pregabalin, benzodiazepines	Eszopiclone, substance P, neuropeptide Y, vasopressin, riluzole, ketamine
PTSD	Psychotherapy, then SSRIs, SNRIs	Second-generation antipsychotics (e.g., quetiapine), prazosin	Mood stabilizers (e.g., tigabine, topiramate, divalproex), beta-adrenergic blockers, D-cyclosterine, ketamine, cannabis, MDMA
Substance use disorder	*Opioids*: Buprenorphine, methadone *Alcohol*: Naltrexone, acamprosate *Tobacco*: Varenicline, bupropion	*Opioids*: Naltrexone *Cocaine*: Amphetamines, modafinil, disulfiram, topiramate, galantamine *Alcohol*: Disulfiram *Tobacco*: Nortryptiline, cysticine (not available in the U.S.)	*Multiple disorders*: LSD, psilocybin, ketamine, MDMA, oxytocin, n-acetylcysteine
*Psychosis**	Second-generation antipsychotics (e.g., quetiapine), first-generation antipsychotic (e.g., haloperidol)	Lumateperone (novel antipsychotic)	Cannabidiol, glutamate modulators, nicotine receptor agonists, D-cyclosterine

*Psychosis may be part of many different disorders, some of which are treated differently than the above.

In the sections below, we group the intrusive thoughts into four broad categories based on their phenomenology, known biological or environmental origins, and involvement of emotional states:

1. Behavioral: intrusive thoughts that take the form of urges and compulsions to engage in repetitive or unwanted actions.
2. Affective: intrusive thoughts that appear to emerge from valenced emotional states, such as anxiety or depression.
3. Substance-induced: intrusive thoughts that are related to psychoactive drugs.
4. Cognitive: intrusive thoughts that involve delusional thoughts and hallucinations.

Intrusive thoughts are rarely a primary target of treatment, and when they are, they are usually treated with psychosocial interventions (e.g., Clark 2005; Ainsworth et al. 2017; van Schie and Anderson 2017; Rebetez et al. 2018; Iyadurai et al. 2019). However, as we note below, a small handful of studies have used pharmacological techniques to reduce intrusive thoughts.

Behavioral

For several disorders, intrusive thoughts take the form of strong urges to engage in harmful, apparently unnecessary, or socially unacceptable actions. This form is a key diagnostic symptom of OCD (Clark and O'Connor 2005) and may include thoughts about engaging in inappropriate sex acts, violence or harm to others, or thoughts related to family members, children, or death. They may also take the form of fear of germs or contamination as well as discomfort at having things out of order, accompanied by urges to act (e.g., cleaning or washing, repeated checking or repeated counting). In the case of body dysmorphic disorder, patients may be obsessively preoccupied with a particular aspect of their appearance and make repeated efforts to alleviate this discomfort by altering their bodies. Patients with OCD may worry about engaging in socially inappropriate behaviors, such as touching or kissing someone inappropriately, hurting someone, or engaging in actions that go against the individual's value system. OCD patients report escalating anxiety as they resist urges to act and a temporary sense of relief after acting on the urge. To varying degrees, intrusive thoughts that relate to urges to engage in socially unacceptable behaviors are also features of other impulsive control disorders, such as eating disorders, gambling, pyromania, kleptomania, and intermittent explosive disorder. In each of these cases, patients become preoccupied by thoughts of engaging in an inappropriate behavior; these thoughts are difficult to control and can interfere with their normal function.

For each of these disorders, selective serotonin reuptake inhibitors (SSRIs) are the first- or second-line of treatment. The behavioral processes through which SSRIs relieve OCD and associated disorders have been studied in some

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depth, but are still not understood. Drugs may reduce anxiety and dampen responses to stimuli that trigger the obsessions, or they may modulate the obsessive thoughts themselves. Tricyclic antidepressants are also used for OCD, and second-line treatments include other serotonin and norepinephrine reuptake inhibitors (SNRIs) with less serotonergic activity (Hirschtritt et al. 2017). Cognitive behavioral therapy is an accepted nonpharmacological treatment for OCD, and there is some support for adjuvant use of neuroleptics, which may be especially helpful in OCD patients with tics, though may not act to reduce obsessive thoughts (Bloch et al. 2006).

Affective

Intrusive thoughts are key features of several affective disorders, which are characterized by strong emotional states such as depression, anxiety, or mania. Patients with major depressive disorder report ruminative intrusive thoughts that are congruent with their negative mood states, such as self-deprecating thoughts of worthlessness or guilt, delusions of guilt, or paranoia in psychotic depression. Patients with generalized anxiety disorder report intrusive thoughts that are congruent with their anxious mood states, such as worries about life, including finances, family, work performance, or accomplishing everyday tasks. In another disorder in which anxiety is a prominent feature, PTSD, intrusive thoughts relate directly to the experienced trauma, typically in the form of vivid memories related to the traumatic event, including the people, context, and emotions experienced. Individuals with PTSD exhibit a heightened sensitivity to cues related to the trauma, which may generalize to other stress-related cues. In PTSD, intrusive thoughts are typically associated with strong negative affect, including both anxiety and depression. The intrusive thoughts themselves are highly distressing and may be accompanied by an urge to act, in the form of fighting or fleeing from the situation. They are also a feature of intermittent explosive disorder in which patients experience explosive outbursts of anger and violence. These may be spontaneous or elicited by inconsequential events perceived as provocation. The final category of mood disorders, those including symptoms of mania, may be accompanied by strong urges or recurrent thoughts that lead to impulsive behaviors, such as financial spending or risky sexual behavior, but it is not clear to what extent these urges are distressing to the individual experiencing them.

In major depressive disorder, intrusive thoughts which occur as part of ruminations are typically treated with SSRIs. While ruminative thoughts are not part of the diagnostic criteria for a major depressive episode, they frequently occur as a part of the disorder. Commonly used instruments, like the Hamilton Depression Rating Scale and the Beck Depression Inventory, do not directly assess ruminative thinking, so little is known about the direct effect of antidepressant medications on these types of thoughts. Future research may

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utilize instruments that specifically assess ruminations, such as the response scale Penn State Worry Questionnaire (Meyer et al. 1990), or specific questions in standardized clinical scales, such as GAD-7 (two worry questions) and PHQ-9 (thoughts of being dead or self-harm). Beyond ruminative thoughts of worthlessness or guilt that may present during a major depressive episode, depression may also have psychotic features, characterized by delusions of guilt and paranoia, and these require different pharmacological treatments. A recent meta-analysis suggested that the most effective treatment for depression with psychotic features consists of combination therapy with both an antidepressant and antipsychotic medication (Wijkstra et al. 2013). While initially there was a concern that novel treatments for depression, such as ketamine, may not be appropriate for patients with psychotic features, due to potentially psychotomimetic effects, case reports have suggested otherwise (Ribeiro et al. 2016).

To address the persistent worries involved in generalized anxiety disorder, SSRIs and SNRIs are first-line treatments. Over the past several years, there has been a shift away from treating such disorders with benzodiazepines due to the higher risk of tolerance and higher rate of withdrawal symptoms seen with this class of medications (Offidani et al. 2013). Other second-line treatments include the azapirone buspirone and pregabalin, both of which may act to reduce persistent worries. Buspirone may also act at 5HT-1A receptors (Howland 2015). Pregabalin, though similar in structure to GABA, may act by binding voltage-gated calcium channels and reducing downstream glutamatergic signaling (Baldwin et al. 2013). Antipsychotics have also been studied in the treatment of generalized anxiety disorder (Gao et al. 2006). Neuropeptides, such as vasopressin and neuropeptide Y, have shown some promise in the treatment of the intrusive thoughts associated with generalized anxiety disorder, based on their efficacy in facilitating fear extinction (Tasan et al. 2016). For many of these treatments, it is not clear whether the medication targets the affective state of fear or the anxious thoughts associated with the disorder, and it can be hard to isolate these components in a research setting. In a promising novel line of research, cancer patients with anxious thoughts related to their terminal illness have been treated with single doses of psychedelic drugs, such as psilocybin or LSD (Griffiths et al. 2016b; Ross et al. 2016). Reportedly, 80% of patients showed a reduction in anxious thoughts after only one to two experiences with the medication. There is an urgent need for further research to determine how single administration of psychoactive substances can induce lasting changes in mood and psychiatric symptomatology.

In PTSD, treatments have focused on blocking different stages of the processing of traumatic memories. Graebener et al. (2017) examined the effect of cortisol on intrusive memories in patients with PTSD but found no effect. Taylor and Torregrossa (2015) discuss the highly promising approach of pharmacologically blocking the reconsolidation of maladaptive and intrusive memories, but this intriguing idea has not yet led to effective treatments. Hill et al. (2017) discuss the possibility of targeting PTSD-related intrusive thoughts

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with drugs that act on the endocannabinoid system, but such medications have not yet reached clinical application.

Drug Induced

In substance use disorders (SUDs), intrusive thoughts are a key feature. They typically take the form of preoccupation with drug use, reactivity to drug-related stimuli, and craving or urges to use drugs. Indeed, "craving" was recently added to DSM-5 (American Psychiatric Association 2013) as a symptom in the diagnostic criteria for SUDs, and it is among the most frequent symptom reported by drug users attempting to quit. Cravings are problematic not only because they predict or presage the occurrence of actual drug use, but also because they can be sufficiently distressing to drug users to be a target of treatment in their own right, independently of actual drug use (Green and Ray 2018). The origin of drug-related intrusive thoughts in SUDs is not fully understood and may be multidimensional, reflecting both underlying physiological conditions and responses to Pavlovian conditioned stimuli. For example, craving is a central feature of acute withdrawal from a drug after regular use, and it is also elicited by drug-related cues in the environment or memories of drug use. Cravings may be elicited in abstinent users, even long after withdrawal, by drug-related stimuli, by positive or negative emotional events, or by ingestion of a small amount of the drug itself. In other cases, cravings or urges occur without any definable precipitant. Whether all these forms of drug-related intrusive thoughts and cravings reflect a single underlying neural process remains unknown. Notably, however, there are intrusive thoughts specific to each drug, and withdrawal from one drug does not induce craving for other drugs.

Although intrusive thoughts are a key feature of SUDs, they are not usually selected as a separate target symptom for pharmacological treatment. Thus, as with other psychiatric disorders, pharmacological treatments for SUDs target the full constellation of the disorder rather than individual symptoms. Further, pharmacological treatments of SUDs are typically specific for the class of drug that is abused (e.g., opioids, nicotine). Nevertheless, several studies have examined the effects of medications specifically on ratings of craving for a particular drug. For example, Courtney et al. (2016) reported that naltrexone (opioid antagonist) blocked conditioned craving to heroin cues, and Green and Ray (2018) reported that varenicline (nicotinic partial agonist) dampened cravings for tobacco cigarettes. In other studies, oxytocin blocked cravings elicited by cues related to both cannabis (McRae-Clark et al. 2013) and tobacco cigarettes (Miller et al. 2016). One promising new pharmacological intervention for SUDs, as well as other psychiatric disorders characterized by intrusive thoughts, is n-acetylcysteine (Dean et al. 2011; McClure et al. 2014; Minarini et al. 2017). N-acetylcysteine is a precursor to the antioxidant glutathione, and it acts as a modulator of glutamatergic, dopaminergic, neurotropic, and inflammatory pathways. Although this

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medication has not been approved for treatment, Dean et al. (2011) review promising results with this drug in the treatment of cannabis use, cigarette smoking, cocaine addiction, and several other psychiatric conditions in which intrusive thoughts play a role. However, larger studies on the effects of n-acetylcysteine for cocaine addiction or cannabis addiction have been disappointing (Mardikian et al. 2007; Gray et al. 2017).

Cognitive

Intrusive thoughts may be a part of several different psychotic disorders in the form of delusions or cognitive distortions. Psychotic disorders, including schizophrenia and schizoaffective disorder, may present with patients experiencing uncontrolled and sometimes disturbing thoughts, images, or perceptions. Delusions, or beliefs that are inconsistent with reality, are the most obvious form of intrusive thoughts manifesting in psychotic disorders. Perceptual hallucinations (auditory, visual, olfactory, tactile) may or may not fall into the category of "thoughts," depending on whether patients recognize them as originating within their own mind. Both hallucinations and delusions are considered "positive symptoms" of these disorders, suggesting that they are additional thoughts and perceptions that patients struggle with, as opposed to "negative symptoms," which reflect a relative deficiency of volition, speech, or other constructs.

The typical treatment of positive symptoms of psychotic disorders consist of second-generation antipsychotic medications. Commonly used second-generation antipsychotic medications, such as olanzapine, ziprasidone, and quetiapine, are remarkably effective at reducing hallucinations in about 92% of patients who take them for a year, though they have many side effects (Sommer et al. 2012). First-generation antipsychotic medications, such as haloperidol, are thought to target and block D2 receptors, while second-generation medications are believed to have complex actions involving D2 receptor blockade and activity at 5HT2A receptors as well (Abi-Dargham and Laruelle 2005). Delusions in schizophrenia and depression appear to respond to antipsychotics, although delusions in delusional disorder and bipolar disorder are less responsive to antipsychotic treatment. One study found that only 22% of psychotic patients with schizophrenia spectrum disorders reported improvement in "cognitive preoccupations" after two weeks of antipsychotic treatment (Mizrahi et al. 2006).

New treatments for intrusive thoughts in psychotic disorders are being investigated. Cannabidiol (CBD), a component of cannabis, has been tested in the treatment of schizophrenia. One recent study showed reductions in positive symptoms of schizophrenia and improved cognition after six weeks of 1000 mg CBD/day adjunctive treatment (McGuire et al. 2018). Glutamate modulators have also shown promise in the treatment of intrusive thoughts in

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schizophrenia (Hashimoto et al. 2013), presumably as a result of the importance of learning and the integration of new information in reducing delusional thought patterns. Glutamate-modulator treatments are being used to facilitate cognitive behavioral therapy, which can be used to target intrusive thoughts. For example, the partial agonist at the glycine site of the NMDA receptor, d-cyclosterine (50 mg), has shown promise in reducing delusional severity in patients with schizophrenia and schizoaffective disorder (Gottlieb et al. 2011). Sodium nitroprusside, another potential NMDA modulator, was not effective in the treatment of schizophrenia (Brown et al. 2019a). More research is needed to determine exactly which pharmacological treatments are effective, and in which contexts.

Neuropharmacological Considerations

It is worth considering the possibility that different neurotransmitter systems play distinct roles in the generation of intrusive thoughts or in the ability to control or treat them. Not surprisingly, given the heterogeneity of the intrusive thoughts described above, almost every neurotransmitter system is implicated in either the generation or the treatment of intrusive thoughts, including dopamine, norepinephrine, serotonin, acetylcholine, glutamate, endogenous opioid, and endocannabinoid systems, as well as hormonal systems such as oxytocin or stress hormones. With respect to the behavioral intrusive thoughts described above, no single neurotransmitter system has been implicated in "impulse control" disorders or OCD (Williams and Potenza 2008). Impulse control disorders, such as pathological gambling, have been linked to serotonin, dopamine (by modulating reward pathways), and norepinephrine dysfunction (arousal and excitement). The pathophysiology of OCD is poorly understood, but serotonergic drugs are commonly used to treat this disorder, and there is evidence that glutamatergic drugs may be effective as well (Goodman et al. 2014). With respect to affective intrusive thoughts, serotonin circuits are most strongly implicated in both the etiology and treatment. Yet other transmitter systems, such as GABA, norepinephrine, and most recently glutamatergic systems, are also implicated. As with the other disorders, little is known about the receptor mechanisms underlying intrusive thoughts, independent of the broader range of symptoms of the disorders. In the case of drug-induced or substance-abuse disorders, the focus of most treatments is on the neurotransmitter system involved with each specific drug (e.g., cholinergic for cigarette smoking, dopaminergic for stimulants). Yet, there is also some evidence that certain pharmacological treatments may target other systems, such as oxytocin receptors or stress hormone receptors. Other possible treatments target the reconsolidation of drug-related memories (cues), independent of the specific drug type. With respect to cognitive intrusive thoughts described above, the dopamine system is most strongly implicated in the pathophysiology of psychotic disorders, and

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drugs that block dopamine function are also the primary basis for pharmacological treatment. As noted above, however, the role of dopamine specifically in intrusive thoughts, separate from other symptoms of psychotic disorders, is not known.

Another consideration in the pharmacological treatment of intrusive thoughts is the temporal characteristics of dosing. Many psychiatric medications, such as antidepressant and antipsychotic drugs, are prescribed for daily use over extended periods of time. Recently there has been a growing interest in medications that can be used with a single or small number of administrations. Examples of these are the use of ketamine for depression and, more controversially, the use of psychedelic drugs in the treatment of anxiety, depression, or substance abuse. How exactly single, high doses of psychedelic or other psychoactive drugs improve persistent psychiatric symptoms is an exciting and challenging new direction of research. Do their effects depend on the psychological experience, or are they related to neuropharmacological changes in brain function? Finally, there is also an important role for drugs used in combination with a behavioral intervention, such as the use of MDMA during psychotherapy sessions or the use of beta-adrenergic blockers during presentation of drug-related memory cues. These different modes of administration of psychiatric medications offer promising new approaches to combining pharmacological with behavioral interventions.

Conclusions

Intrusive thoughts are symptoms of a wide range of psychiatric disorders with markedly different pathophysiology, and they take many forms: from the urge to act, ruminations, and cravings to delusional thoughts. Perhaps because they are associated with so many different disorders, each with a different pathophysiology, a wide range of medications have been used to treat intrusive thoughts. Given the heterogeneity of their symptoms and associated disorders, it is unlikely that any single neural circuit mediates intrusive thoughts, or that any single medication can be used to target them across diagnostic categories. Nevertheless, there may be commonalities associated with different disorders (e.g., cravings of food in eating disorders or drugs in SUDs). Some intrusive thoughts may be mainly a disorder of memory (e.g., symptoms in PTSD or addiction), whereas others originate from disordered cognition or strong emotional states. By examining intrusive thoughts both within and across disorders, it may be possible to identify underlying processes that could be targets for new pharmacological treatments.

A handful of issues warrant consideration in studying pharmacological interventions for this elusive symptom. Although certain medications are classically associated with certain psychiatric disorders, in practice a wide range of medications are used, even for the same disorder. For example, dopamine

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antagonists are typically the first line of treatment for schizophrenia or serotonin reuptake blockers for depression, yet physicians often sample from a range of medications on an individualized basis to find effective treatments. The range of pharmacological treatments is partly because patients vary in their response to medications, as well as because the symptoms within a disorder vary across individuals and over time. Further, diagnoses and disorders are in reality the composite of individual symptoms, and thus the individual symptoms are rarely the target of medication development. It is thus difficult to determine which medications are effective specifically for an individual symptom, such as intrusive thoughts. Further, most psychiatric medications target a constellation of symptoms involved in the disorder rather than any specific symptom. For example, SSRIs are prescribed for depression to improve all the components of the disorder, which may include mood, sleep, appetite, and energy levels. This makes it difficult to examine published studies into the efficacy of various medications in the treatment of intrusive thoughts. Prospective, controlled studies with specific intrusive thought-related outcome measures are necessary as a next step in investigating these questions.

We conclude with a comment about the recent introduction of a novel form of pharmacological treatment for psychiatric disorders: the use of single, high doses of "psychedelic" drugs. Drugs such as ketamine, MDMA, and psilocybin, which were formerly only considered in the context of nonmedical use, are now being tested in therapeutic settings. Remarkably, these drugs appear to be effective after just one or two single administrations, in contrast to other medications that are used on a daily basis. It remains to be determined how single doses of these drugs can produce lasting beneficial effects on, for example, major depression, end-of-life anxiety, or PTSD. It also remains to be determined whether, and how, these novel treatments affect intrusive thoughts in particular. This is an exciting and promising new direction for psychiatric medications.

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