CHAPTER TWELVE

Pharmacologic Treatment of Intermittent Explosive Disorder

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Contents

This chapter will cover the pharmacological treatment of Intermittent Explosive Disorder (IED) and impulsive aggression. It will primarily focus on the treatment of impulsive aggression in adults. The first section will review the theoretical and clinical framework of pharmacological treatment. The second section will review data from randomized, placebo-controlled trials of pharmacological approaches. The third and final section will review ethical, regulatory, and safety issues.

Theoretical Considerations in the Pharmacological Treatment of IED and Impulsive Aggression

A useful heuristic for classifying aggression in the clinic is to divide aggression into three main types: premeditated or "cold" aggression, frustration-based aggression, and impulsive aggression. This heuristic is useful even in cases where the IED diagnosis has been established. Premediated aggression, when part of a recurrent pattern, is most closely associated with antisocial personality disorder and psychopathy. Its goal often is monetary gain or social dominance. Anger may be expressed as part of the aggressive

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act, especially when the aggressive act has components of reactive, or impulsive aggression, such as those acts of aggression associated with revenge. Rarely, premediated aggression may be motivated by the pleasure experienced by causing suffering, as was once captured in DSM-III by sadistic personality disorder (Myers, Burket, & Husted, 2006) and Sexual Sadism Disorder. Generally, premeditated aggression is more difficult to treat and guidance from the empirical literature is scant. Additionally, the treatment frame is more likely to be forensic or compulsory; this is because in the absence of such a framework, treatment recommendations will not be followed. Because of a tendency toward deception, collateral sources of information are needed to corroborate self-reported symptoms. These are frequently the potential victims or legal entities entrusted with their protection. Thus the clinician in these cases is usually working as part of a team, with administrative or forensic components. Frustration-based aggression is most closely associated with developmental disorders, dementia, and neurological syndromes. It is by nature impulsive, but its triggers are rarely social. Its treatment frequently involves management of contingencies, but may also require psychopharmacological approaches when severe. The clinician in these cases is usually working with a family system or other custodial caregiver. Frequently, the patient with frustration-based aggression is unable to give consent for treatment, lacking the mental capacity for consent.

In contrast, the clinical treatment of IED is typically motivated by the patients themselves. Impulsive aggression is largely a social behavior, typically provoked by a social interaction. Because humans are social creatures, whose social identities are defined by their social context, disruptions of this social context by outbursts of anger and aggression incur a heavy cost over time. Naturally, this cost is shared by the patient as well as the "victims" of aggression: family members, friends, coworkers, and sometimes strangers. However, it is not unusual for the patient to be most aware of the cumulative cost of a lifetime of unnecessary outbursts of anger in the form of wrecked relationships, serious problems at work, or the legal ramifications of impulsive acts. In our experience, it is this self-awareness that facilitates and makes possible the treatment of IED (Steakley-Freeman, Lee, McCloskey, & Coccaro, 2018). In simple terms, many patients with IED willingly come in to the clinic and look for help. There are important caveats to this optimistic perspective. IED and impulsive aggression may coexist with predatory, premediated forms of aggression in certain contexts, such as domestic or child abuse. These can be considered special cases that have more in common with the treatment of premeditated aggression, discussed

in the section on antidepressants. Because of the negative consequences of impulsive aggression, persons with IED may feel shame about their behavior. In the absence of a therapeutic relationship, minimization and denial are likely to be encountered. However, when a sufficient degree of trust exists, the clinician can assess impulsive aggression using a clinical interview. Impulsive aggressive individuals are by definition *probabilistically* inclined to aggressive behavior, its treatment usually voluntary, thus requiring informed consent. Fortunately, IED usually occurs in individuals who are able to give informed consent. We highlight this fact because no pharmacological approaches for impulsive aggression have FDA approval. Thus an important initial step in the consent process is informing the patient that any proposed treatment is off label, even when based on evidence from gold-standard randomized clinical trials. Failure to do risks ethical violation and legal liability.

Diagnosis of IED is done by clinical interview. Establishing whether the aggression is disproportionate to the provocation can be done by assessing if the aggression was initiated by the patient or if the patient increased the level of aggression. In DSM-5, IED can be staged by A_1 or A_2 criteria. Criterion A_1 describes recurrent verbal aggression or mild, noninjurious assault. Criterion A_2 describes recurrent physical assault (Coccaro, Lee, & McCloskey, 2014). Clinical interview should also rule out boundary conditions but include frequently comorbid conditions, such as personality disorder. A subtle but important issue in the diagnosis of IED is the question of comorbidity between IED and Borderline/Antisocial Personality Disorder (BPD/ASPD). Although DSM-5 suggests that BPD/ASPD can be considered an exclusionary condition (Criterion F), empirical data reveal that when the diagnostic criteria for both conditions are met, the IED diagnosis remains an important predictor of aggressive behavior (Coccaro, 2012). In fact, approximately 43% of individuals with IED may have comorbid BPD and/or ASPD (Coccaro, Shima, & Lee, 2018). Data from clinical trials suggest that interview measures of aggressive behavior may be more sensitive than self-report-based questionnaire measures to change, possibly due to the time lag before individuals recognize a change in their actual behavior (Coccaro, Berman, & Kavoussi, 1997). Tracking of aggression can be done using the Overt Aggression Scale-Modified (OAS-M; Coccaro, Harvey, Kupsaw-Lawrence, Herbert, & Bernstein, 1991). Another option is for the patient and/or family member to journal the frequency and severity of their aggressive behavior on a weekly basis. Use of such systematic measures can enhance the ability of the clinician to make informed decisions about treatment.

Psychopharmacological Approaches

After establishing the treatment framework and deciding to use medication, the choice of which medication to use can be guided by the available evidence. Treatment guidelines for impulsive aggression specifically are scarce. One recent review proposed a two-step treatment algorithm (Felthous & Stanford, 2015) that relies on clinical staging. Less severe aggression (corresponding broadly to DSM-5 IED A_1 Criterion), they argue, should first be treated with selective-serotonin reuptake inhibitor (SSRI) fluoxetine. If fluoxetine does not work, the next step would be a trial of an anticonvulsant or lithium. More severe aggression, corresponding to DSM5 IED A_2 Criterion, should be treated with an anticonvulsant or lithium, skipping fluoxetine. An exception to this may be severe aggression seen in the context of Cluster B personality disorder, in whom fluoxetine may remain the first choice. These recommendations are based on a reasonable interpretation of the literature and are useful. However, it is important to point out that the comparative trials between these agents are lacking. In their absence, it is impossible to know which approaches will be most effective for a given patient. Therefore we would argue that treatment decisions at this point should be informed by weighing the potential benefits of treatment versus the potential side effects in a given patient, rather than by a priori assumptions of differential efficacy. Operationalization of this decision making will be provided at the conclusion of this chapter. This next section will review the evidence for each drug class: SSRIs, mood stabilizers and anticonvulsants, benzodiazepines, and neuroleptics. For the sake of brevity, only the results of randomized controlled trials are discussed (Table 1).

SSRI Treatment of IED

The now replicated association of IED with serotonergic dysfunction (Yanowitch and Coccaro, 2011) establishes the biological plausibility of using SSRIs in the treatment of aggression. Of the SSRIs, the most evidence for efficacy has accumulated for fluoxetine. The first randomized, double-blinded, placebo-controlled trial (RCT) in IED was conducted in 40 adults with personality disorder (Coccaro & Kavoussi, 1997). In it, fluoxetine was superior to placebo as early as the end of the first month and continued to be superior to placebo in reducing aggression in the second and third months of treatment. Twenty to forty milligrams of fluoxetine reduced verbal and indirect aggression; no effect was seen on direct physical aggression, but such

Table 1 Randomized Clinical Trials IED and Impulsive Aggression

SSRI	Patient Type	N	Trial Type	Drugs	Results
Salzman et al., 1995	BPD	23	RCT	Fluoxetine vs. Placebo	Fluoxetine reduced OAS anger
Coccaro, Kavoussi, & Hauger, 1997	Personality disordered male and female adults with IED	40	RCT	Fluoxetine vs. Placebo	Fluoxetine reduced OAS-M Aggression and OAS-M Irritability
Coccaro et al., 2009	Personality disordered male and female adults with IED	100	RCT	Fluoxetine vs. Placebo	Fluoxetine reduced OAS-M Aggression and OAS-M Irritability
Silva et al., 2010	Borderline Personality Disordered	59	Open-Label	Fluoxetine Alone	Fluoxetine reduced OAS-M Aggression and OAS-M Irritability from Baseline to End of Study; Response observed only in those with the 5-HTT *ll* Genotype
George et al., 2011	Alcoholics with Intimate Partner Violence	24	RCT	Fluoxetine vs. Placebo	Fluoxetine reduced OAS-M Irritability
Coccaro et al., 2015	Personality disordered adults with IED	90	RCT	Fluoxetine vs. Divalproex vs. Placebo	Null results
Lithium					
Sheard et al., 1976	Prisoners with impulsive aggression	66	RCT	Lithium vs. Placebo	Decreased disciplinary sanctions
Anticonvulsants					
Barratt et al., 1997	Inmates with aggression	$N=60$	Double-Blind Randomized Controlled Trial (RCT)	Phenytoin vs Placebo	Phenytoin reduced impulsive aggression

Continued

Table 1 Randomized Clinical Trials IED and Impulsive Aggression—cont'd

SSRI	Patient Type	N	Trial Type	Drugs	Results
Stanford et al., 2001	Men with impulsive aggression	46	RCT	Phenytoin vs Placebo	Phenytoin reduced OAS aggression
Stanford et al., 2005	Men with impulsive aggression	28	RCT	Phenytoin vs Carbamazepine vs Valproate	Valproate and phenytoin > Carbamazepine > Placebo
Hollander et al., 2003	Cluster B IED PTSD	246	RCT	Divalproex 500–3000 mg vs. Placebo	No significant effect on OAS-M score
Mattes, 1990	Adults with IED and aggression	51	Single-blind, randomized trial	Carbamazepine vs. Propranolol	Carbamazepine but no propranolol reduced aggression in IED
Mattes, 2005	Outpatients with impulsive aggression	48	RCT	Oxcarbazepine vs Placebo	Oxcarbazepine reduced OAS aggression
Mattes, 2008	Outpatients with impulsive aggression	40	RCT	Levetiracetam vs. Placebo	Null results

events were rare and the statistical power to detect an effect was lacking. The beneficial effect of fluoxetine was restricted to interview measures of aggression but not a questionnaire measure (Anger, Irritability, and Assault Questionnaire; AIAQ). This may because the AIAQ asks for aggressive tendencies, the change in perception of which may lag in IED subjects. Notably, the antiaggressive effects were not due to reduced depression or anxiety.

In a larger sample of 100 adults with IED and personality disorder, fluoxetine was again found to be superior to placebo for aggression and irritability, and once again were not due to changed depression or anxiety (Coccaro, Lee, & Kavoussi, 2009). By the end of the study, 46% of fluoxetine-treated subjects were remitted from IED. Effects were seen as early as 2 weeks. The results of these two studies back up positive results on anger in an earlier RCT of fluoxetine in the treatment of 23 adults with BPD (Salzman et al., 1995) and also predated two other studies (George et al., 2011; Silva et al., 2010) that reported the antiaggressive effect of fluoxetine in adult individuals with history of impulsive aggression.

Not all trials have been positive. A double-blind, randomized comparison of fluoxetine, valproate, and placebo found that neither fluoxetine nor divalproex was superior to placebo in treating aggression. A secondary analysis revealed that beneficial effects of fluoxetine relative to placebo were seen only in highly impulsive aggressive subjects (OAS-M Aggression $\geq$15; OAS-M Irritability $\geq$6; Coccaro, Lee, Breen, & Irwin, 2015).

The clinical finding that fluoxetine reduces aggression in IED, particularly in highly aggressive individuals, has been supported by experimental research. In animal models, fluoxetine has been found to reduce aggression (Fuller, 1996). In humans, SSRIs have been associated with reduction of aggressive behavior in laboratory paradigms both when administered chronically (Cherek, Lane, Pietras, & Steinberg, 2002) and acutely (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009) for those with a history of aggressive behavior.

Unfortunately, no other SSRIs have been tested in IED with rigorous RCTs though negative results on anger have been found for the effects of fluvoxamine relative to placebo in the treatment of BPD (Rinne, van den Brink, Wouters, & van Dyck, 2002).

Predictors of Response

There are no confirmed predictors of SSRI response. Preliminary information, as reviewed before, points to greater severity of aggression and

irritability (Coccaro et al., 2015), higher pretreatment neuroticism and lower harm avoidance (Phan, Lee, & Coccaro, 2011), and greater pretreatment 5-HT function (Coccaro & Kavoussi, 1997). Additionally, preliminary data suggests that treatment-related suppression of amygdala activation to anger faces is linearly related to a more favorable antiaggressive response to either fluoxetine or divalproex (Coccaro et al., 2015). Pharmacogenomics holds great promise in predicting treatment response, but very little is known about this. Preliminary results from a pharmacogenetic study in 59 adults with borderline personality disorder suggest that individuals with long arm of the serotonin transporter are more likely to respond to fluoxetine in the treatment of aggression (Silva et al., 2010). Developmental stage may also determine the effect of SSRI medications on aggression, with adolescent patients, but not adult patients, more likely to suffer from increased aggression after the initiation of SSRI treatment (Halperin et al., 1997; Sharma, Guski, Freund, & Gøtzsche, 2016).

Anticonvulsants and Mood Stabilizers

Given the role of intense affective states in aggression, anticonvulsants and mood stabilizers have been studied as potential pharmacological treatments. The first, and often cited, research examining this question was a double-blind, crossover study of lithium vs. placebo in 66 incarcerated adolescent and young adults with history of impulsive aggression (Sheard, Marini, Bridges, & Wagner, 1976). Lithium was found to reduce the number of aggression-related infractions in this severe, forensic population.

Phenytoin has also demonstrated some efficacy at improving impulsive aggression specifically. In a study involving 60 incarcerated participants, phenytoin reduced impulsive, but not premedicated aggression (Barratt, Stanford, Felthous, & Kent, 1997). Supporting the potential utility of phenytoin for IED specifically, a double-blind placebo-controlled study was conducted in 46 men who met DSM-IV A and B criteria for IED (i.e., several episodes of discrete aggression disproportionate to the precipitating stressor) (Stanford et al., 2001). Individuals treated with daily phenytoin significantly decreased the number of weekly aggressive outbursts when compared to placebo and reported subjectively reduced anger and hostility. In aggregative, meta-analysis reveals that across studies, phenytoin reduces impulsive aggression with large effect size SMD = 1.34 (72.16–70.52; Johnson et al., 2014).

A case series has been reported of the positive effects of adjunctive carbamazepine in highly aggressive and treatment refractory psychotic adults with severe aggression (Young & Hillbrand, 1994). A randomized, single-blind comparison of carbamazepine and propranolol in adults with impulsive aggression and IED found carbamazepine to be superior in reducing rage outbursts (Mattes, 1990). Both drugs were safe. Interestingly, an IED diagnosis predicted better outcome with carbamazepine. These results are consistent with positive effects of carbamazepine on behavioral outbursts in BPD (Cowdry & Gardner, 1988).

Oxcarbazepine was developed as a modification of carbamazepine to eliminate hepatic and immune-related serious side effects. Oxcarbazepine is derived from carbamazepine by substitution of a carbon-carbon double bond on the dibenzazepine ring. In an RCT in adults with IED, oxcarbazepine reduced OAS aggression and was associated with higher patient-rated improvement compared to placebo (Mattes, 2005).

Further, although the anticonvulsant divalproex has decreased aggression and irritability in individuals with a personality disorder, it was no better than placebo at reducing aggression in IED (Hollander et al., 2003) in a study that was largely negative. These results, when combined with results from a previous RCT in BPD, suggest that divalproex has positive effects in BPD, but perhaps not in IED that is not comorbid with it. Negative results have also been reported for levetiracetam (Mattes, 2008).

Some preliminary statements can be made on predictors of individual differences in response to mood stabilizers and anticonvulsants. In terms of serious toxicity, the FDA has warned about the relationship between HLA-B*1502 and Stevens-Johnson syndrome with carbamazepine. It has also warned against using phenytoin as a substitute. While divalproex may be of use in BPD, in IED outside of this, it may not work. Phenytoin has been found to reduce aggression in severe cases of IED and is a potential choice in difficult cases. Carbamazepine has been found to reduce aggression in IED but not in ADHD.

Benzodiazepines

Benzodiazepines have been found to increase laboratory-measured aggression acutely in aggressive individuals (Berman & Stuart, 1995). Controlled data in BPD have found that alprazolam increased behavioral outbursts (Cowdry & Gardner, 1988). Somewhat counterintuitively, the scant literature that exists is not supportive of the use of benzodiazepines in IED.

This, combined with their potential for abuse, and the threat of death in overdose with narcotics, means that benzodiazepines are not likely to be effective in IED.

Antipsychotics

Somewhat surprisingly, there is no direct evidence of the efficacy of antipsychotic medications in IED. This is contrast to the FDA indication for irritability in children and adolescents with autism. In BPD, metaanalytic research reveals that antipsychotics worsen global severity (SMD = 0.3, 95% CI −0.22 to 0.82). However, pooled results from two studies ($n = 114$) reveal it does reduce anger intensity (SMD = −0.46, 95% CI −0.84 to −0.09(Lieb et al., 2010). Like haloperidol, olanzapine too reduces anger with a small effect size, when data from 631 patients and 3 trials are pooled (mean change SD −0.27, 95% CI −0.43 to −0.12). (Stoffers et al., 2010). In an RCT with 96 BPD outpatients, low dose of quetiapine reduced OAS-M aggression score compared to placebo (Black et al., 2014). In the context of psychotic disorders, evidence suggests that clozapine is the most effective antipsychotic medication approach to aggression (Citrome et al., 2001). Its antiaggressive effect was not immediate, but was independent of its effect on psychotic symptoms (Volavka et al., 2004). Evidence to support the use of atypical antipsychotics in the treatment of IED is scant. In boundary conditions, such as BPD and psychosis, the evidence indicates that antipsychotics reduce aggression but may not treat other aspects of the disorder, with serious side effects to consider.

Safety Considerations and Rational Approaches to Psychopharmacology

Managing a population of patients, it becomes plainly apparent that IED usually exists in a health/medical context. Medication interactions, risk of pregnancy, and toxicity require a careful approach when assessing the risks in relation to benefits of "off-label" medication prescribing.

Cytochrome P450 interactions with concomitant medications are not uncommon, especially in the aging population. Such interactions can alter the dose-response relationship with respect to side effects and toxicity. For fluoxetine, CYP2D6 inhibition makes coprescribing with antihistamines, muscle relaxers, tricyclic antidepressants, antipsychotics, and beta-blockers more technically difficult. Some of the potential CYP2D6 interactions could lead to prolongation of the cardiac QT interval, and thus would require

serial EKG monitoring. Fluoxetine can trigger mania or hypomania in patients with bipolar disorder, or those who are susceptible to it. Discriminating the outbursts of IED from manic-related behaviors of bipolar disorder can be difficult, especially in retrospect.

For carbamazepine and divalproex, both CYP3A4 induction and inhibition can be problematic. Complex, system-level interactions make using carbamazepine and divalproex in women of childbearing age difficult to manage, as the oral contraceptive is metabolized more quickly due to protein binding issues. The relevance of pharmacogenomic testing of genetic variation in the CYP isoenzyme polymorphisms remains uncertain but will likely turn out to be of importance. A promising harbinger of this future is the availability of testing for HLA-B*1502 to reduce the risk of toxic epidermal necrosis (TENS) with carbamazepine and phenytoin.

Should treatment approaches be guided by risk profiles? If so, then a few possibilities come to mind. Firstly, females of childbearing age with IED may be easier to manage on an SSRI such as fluoxetine, rather than an anticonvulsant or atypical antipsychotic. Secondly, patients with a history of bipolar disorder or where it is strongly suspected should probably not receive an SSRI in the absence of a mood-stabilizing drug. If genetic testing reveals HLA-B*1502, an SSRI would be preferable.

This returns us to the issue of psychopharmacological treatment algorithms for IED. We previously discussed using clinical staging to guide the first line treatment of aggression in IED, in which IED cases meeting A1 criteria receive fluoxetine, and those meeting A2 criteria receive either carbamazepine or phenytoin. The clinical principles of the Felthous & Stanford two-step treatment algorithm (Felthous & Stanford, 2015) are sound and applicable to the population clinicians will treat. Integrating these with a rational approach to risk profiling may be the most practical approach. In such a scenario, females of childbearing age should probably receive a trial of fluoxetine before an anticonvulsant, regardless of IED criterion.

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