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The pharmacotherapy of clinical aggression in criminal offenders

La farmacoterapia delle condotte aggressive di interesse clinico negli autori di reato

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Abstract
Pharmacotherapy of clinical aggression begins with assessment of the individual regarding the nature of the aggression and diagnosis. In general psychiatry, but especially in the treatment of criminal offenders, addressing aggressive behavior as well as the mental disorder is essential for safe and effective treatment. Assessment and pharmacotherapy of impulsive aggression is informed by diagnosis, identification of evidence-based anti-impulsive aggressive agents (AIAAs), AIAAs risks and side effects, severity of aggression, prescription parsimony, pharmacotherapy history, and affordability and availability. Pharmacotherapy of aggression that is secondary to a mental disorder must address both the aggressive behavior and the disorder. Illustrative examples discussed here are the pharmacotherapy of aggression secondary to bipolar disorder, schizophrenia and psychotic disorders, and traumatic brain injury respectively.

Key words: aggressive behavior • criminal offenders • mental disorder • assessment • pharmacotherapy

Riassunto
La farmacoterapia dell'aggressività di interesse clinico inizia con la valutazione della sua natura e la diagnosi del disturbo che ne è eventualmente all'origine. E ciò nell'interesse dell'efficacia del trattamento e della sicurezza, specie in abito psichiatrico-forense.
La corretta valutazione e la farmacoterapia dell'aggressività impulsiva, sono infatti sostenute da un corretto processo diagnostico e dalla conoscenza, evidence-based, dei farmaci da utilizzare: la loro efficacia, gli eventuali effetti collaterali, il dosaggio minimo da usare, la loro affidabilità e disponibilità, eventuali trattamenti pregressi, oltre che dall'apprezzamento della severità della condotta aggressiva.
La farmacoterapia delle condotte aggressive secondarie ad un disturbo mentale, deve necessariamente indirizzarsi al trattamento della condotta e del disturbo che ne è alla base. Qui saranno affrontati tipici esempi di condotte aggressive secondarie a disturbo bipolare, a disturbo schizofrenico ed altri dusturbi psicotici, e secondarie a traumi cranici.

Parole chiave: condotta aggressiva • autore di reato • disturbo mentale • valutazione clinica • farmacoterapia

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Introduction

Not all aggression is clinical and not all clinical aggression is best treated with pharmacotherapy. Nonetheless in the treatment of criminal offenders, aggressive behavior should be assessed as well as their mental disorder(s), for safe and effective treatment. Most clinically relevant aggression is impulsive and may be amenable to pharmacotherapy or secondary to a mental disorder. Therefore treatment must begin with an assessment of the nature of the aggressive behavior as well as other primary psychopathology.

1. Assessment of Clinical Aggression

The aggression of the criminal offender must first be evaluated before developing a pharmacotherapeutic strategy (Felthous, 2013). Of the four basic approaches to the assessment of clinical aggression – diagnostic, behavioral, actuarial and phenomenological – (Felthous, 2010), the two most useful approaches for pharmacotherapy are diagnostic and phenomenological. The diagnostic approach to assessing clinical aggression is criticized as being less accurately predictive of future violence in comparison with the actuarial approach, yet it is the most used and most useful approach in psychiatric practice (Felthous, 2014). For example where violent behavior is secondary to mania, once bipolar disorder is diagnosed treatment with a mood stabilizer quells the manic symptoms including the risk of aggressive behavior (El-Mallakh, Roberts, & El-Mallakh, 2008; Felthous, 2010; Moeller & Swann, 2007; Tardiff, 2007).

The second most useful, but probably underused, approach to the assessment of clinical aggression is phenomenological, i.e. assessment of the nature of the aggression regardless of diagnosis. In theory ontogenetic, in practice this approach is descriptive and therefore termed phenomenological (Felthous, 2010). Phenomenological assessment addresses the dichotomous distinction between impulsive and premeditated aggression.

Assessment can be assisted with the structured interview developed by Stanford and Barratt, 1992, or by a version modified by Felthous and colleagues (2009), that relies on written records when the subject is an unreliable informant of his or her violent episodes. The phenomenon of impulsive aggression, well researched and described in the scientific literature, corresponds with intermittent explosive disorder whose criteria has been expanded in DSM-5.

2. Pharmacotherapy of Primary Impulsive Aggression

The aggression of criminal offenders is often primary impulsive aggression. Effective treatment and prevention of this behavior can go a long way towards improving the offender's adaptation to society and within prison systems, reducing physical harm that would otherwise be inflicted upon others and themselves. Nonpharmacotherapeutic measures, such as cognitive-behavioral therapy, have been shown to be effective and are indicated (Deffenbacher, 2003; McClosky, Nobeltt, Deffenbacher, Gollan, & Coccaro, 2008). Nonetheless optimal treatment often requires the use of an anti-impulsive aggressive agent (AIAA, Felthous, 2013).

The diagnostic approach, i.e., the medical model, informs efficacious treatment of manifestations of the disorder including abnormal aggression (Felthous, 2010). With the diagnostic approach, the clinician first assesses the patient's mental condition and diagnosis any presenting mental disorder, using standardized nomenclature such as that of the DSM-5 (American Psychiatric Association, 2015). Next an attempt is made, following the phenomenological approach, to assess the nature of the aggressive behavior, and the presence, severity and frequency of rage episodes of impulsive aggression in particular.

Impulsive aggression is defined as "a 'hair-trigger' response to a stimulus which results in a sudden agitated state that lasts from a few minutes to several hours (Elliot, 1990); the agitation builds to a crescendo and culminates in an aggressive act. During this state, interpersonal communication appears inefficient, and recall of the related events may be poor" (Felthous & Barratt, 2003, p. 130).

3. The Pharmacotherapy of Primary Impulsive Aggression

No anti-impulsive aggressive agent (AIAA) has been approved by the United States Food and Drug Administration for the treatment of impulsive aggression or intermittent explosive disorder. Therefore the treating clinician may decide to first attempt psychotherapy or environmental manipulation (Felthous, 2013). Particularly where the aggression is severe or nonpharmacotherapeutic measures have failed, an AIAA trial is indicated.

The first step in the treatment of primary impulsive aggression is accurate diagnosis of the condition. Assessment includes a description of the nature, severity and frequency of aggressive episodes as well as ideally a diagnosis of co-occurring personality disorder (Felthous, 2013). Next the clinician should obtain a medical history and look for prior use of psychotropic or anti-impulsive aggressive agents, with attention to their favorable effect or impulsive aggression as well as any side effects. If an AIAA has been tried before

with improvement in impulsive aggression, this agent may be selected as the treatment of choice.

Circumspection is warranted because none of the AIAAs are FDA approved for impulsive aggression. One must be especially vigilant against side effects either from the patient's history or during the course of treatment. Monitoring the patient's condition for reduction in aggressive episodes is important and more easily accomplished where the patient is imprisoned or an inpatient of a forensic hospital (Felthous, 2013). If the patient is treated as an outpatient, engagement of a co-inhabiting collateral source such as a spouse who can provide ongoing objective reports is recommended.

Felthous and Stanford (2015) proposed an algorithm for selecting an AIAA for the treatment of primary impulsive aggression in individual patients. The critical factors in this algorithm are: clearly define and characterize the aggressive behavior, identify those drugs with demonstrated efficacy in treating primary impulsive aggression through drug trials of sufficient quality, consider the risks, side effects, and contraindication for each AIAA with regard to the patient, assess the severity of the patient's aggressive outburst, and identify any co-occurring mental or medical condition that might also benefit from one of the AIAAs (Felthous & Stanford, 2015).

4. Diagnosis of Primary Impulsive Aggression

The first step, discussed above, is diagnosing primary impulsive aggression or its closest DSM condition, Intermittent Explosive Disorder (American Psychiatric Association, 2013). Its opposite, premeditated aggression, that is not impulsive is not expected to respond to an AIAA (Barratt et al., 1997a, 1997b). (For further information on the diagnosis of PIA, the reader is referred to Barratt et al. 1997a, 1997b; Stanford & Barratt, 1992; Felthous & Barratt, 2003; the DSM-5 criteria for IED (2013) or a reasonable modification of the IED criteria such as those used by Coccaro (Coccaro & Kavoussi, 1997; Coccaro, Kavoussi & Berman et al., 1998; Coccaro, Lee, & Kavoussi, 2009; Coccaro, 2011).

4.1 *The Anti-Impulsive Aggressive Agents (AIAA)*

Once impulsive aggression is diagnosed the next question is which agents are efficacious in treating it. No agent has been subjected to every phase of research that is necessary to gain approval by the U.S. Food and Drug Administration (FDA) for this indication. Nonetheless efficacy of five drugs has been demonstrated by at least two double-blind control studies. Felthous and colleagues reviewed the literature and identified 55 peer-reviewed studies on the pharmacotherapy of aggression. Each study was assessed using specific quality measures. Levetiracetam had negative results, so not all anticonvulsants are anti-impulsive aggressive agents. Those agents that were shown to be efficacious in at least two higher quality studies were: fluoxetine, phenytoin, carbamazepine/oxcarbazepine, valproate/divalproate, and lithium (Felthous, Lake, Rundle, & Stanford, 2013). Thus the selection of the best AIAA for a patient's primary impulsive aggression would come from these drugs.

4.2 *Risks and Side Effects*

Fluoxetine

The steps that follow need not be in any particular order. A critical consideration is the risks, side effects and contraindications of each of the AIAAs. Of all the AIAAs, fluoxetine has the most favorable side effect profile and is most conveniently administered because serum levels and other laboratory tests are not necessary.

As a rule AIAAs, including selective serotonin reuptake inhibitors (SSRIs) (Goldstein, Carbin, & Sundell, 1997) should be avoided in pregnant females for the treatment of PIA because of the risk of fetal abnormalities. Fluoxetine poses risk so if drug-drug interaction through the P450 system. If the patient must take another SSRI AIAA drug with a risk of drug-drug interaction with fluoxetine the clinician might well consider sertraline for which there is some, but less evidence of efficacy and which shows less, yet some drug-drug interaction via the P450 system. Or the physician may select another AIAA that does not interact with the other drug.

Valproate/Divalproex

Compared with lithium and the other anticonvulsant AIAAs, valproate/divalproex has a favorable side effect profile and would be commonly used for PIA. Because of the risk of neural tube defects it should not be used to treat impulsively aggressive women in the first trimester of their pregnancy (Bowden, 2004; Dreifus, Langer, Moline, & Maxwell, 1989). (Polycystic ovary syndrome is an increase risk for women treated with valoproate/divalproex.) It is not recommended for epileptic women with intellectually development disorder because of their increased risk of pancreatitis, and it should be used only with caution in offenders with intellectual disability (Buzan, Firestone, Thomas, & Dubovsky, 1995). Administration together with other antiepileptics is associated with an increased risk of hepatic failure. It should be avoided in patients with impaired liver functioning (Dreifus et al., 1989; Buzan et al., 1995). Women should be tested for pregnancy prior to the administration of valproate/divalproex (Felthous, 2013).

Carbamazepine

As with AIAAs generally carbamazepine should be avoided in pregnant women due to its heightened risk for low birth weight and teratogenic effects such as craniofacial deformities, digital hypoplasia and spina bifida (Jones, Lacro, Johnson & Adams, 1989; Ketter, Wang, & Post, 2004; Rosa, 1991). As for valproate/divalproate, women should be tested for pregnancy before prescribing (American Psychiatric Association, 2002a). Nursing mothers should be advised not to breastfeed their baby when carbamazepine is prescribed because it transfers into breast milk at half the concentration as that in maternal blood (Froescher, Eichelbaum, Niesen, Dietrich, & Rausch, 1984; Kuhnz et al., 1983). Because of the risk of carbamazepine-associated hyponatremia, carbamazepine and resulting confusion, carbamazepine should be used with caution, if at all, in elderly patients (Ketter et al., 2004).

Although not contraindication, some risks require special vigil and when prescribing carbamazepine: Stephen-Johnson syndrome, agranulocytosis aplastic anemia ("Carbatrol", 2003;

"Tegretaol", 2003), hepatitis, and impaired cardiac condition (Ketter et al., 2004), although the latter is less of a risk than for lithium (Connell, Rappeport, Gordon, & Brodie, 1984; Joffe, Post, Ballenger, Rebar, & Gold, 1986). Any patient with a cardiac history should have an EKG before carbamazepine/oxcarbazepine is prescribed (American Psychiatric Association, 2002a). Because patients of Asian ancestry have an elevated risk of epidermal necrosis and Stephen-Johnson syndrome (Winner, 2013), an alternative AIAA would be preferred for this population.

Phenytoin

Phenytoin's side effects are dose related (Trescher & Lesser, 2008). Because it is prescribed for PIA at a lower dose and serum level than what is needed for seizure control, the side effects should be less likely (Felthous, 2013). A side effect to consider when selecting an AIAA is its impairment of vitamin D absorption (Trescher & Lesser, 2008) leading to complications of hypocalcemia such as osteoporosis. For this reasons phenytoin is not the best AIAA for elderly, nonambulatory, or postmenopausal offenders. Phenytoin should not be prescribed for pregnant female offenders because of the risk to fetal development because of impaired folate metabolism caused by phenytoin. Phenytoin should not be coadministered with a contraceptive agent because it can render contraception ineffective (Trescher & Lesser, 2008), a concern that is especially applicable to offenders who are living in the community. Other side effects to monitor for include gingival hyperplasia, hirsutism, hypersensitive skin reaction, coarsening facial features, neurotoxicity and megaloblastic anemia (Trescher & Lesser, 2008).

Lithium

Although good evidence supports the use of lithium in the control of PIA (Campbell et al., 1984, 1995; Malone et al., 1998; Jones, Arlidge, Gilham, Reagu, van den Bree, & Taylor, 2011; Sheard, Marini, Bridges, & Wagner, 1976). Lithium should be avoided in the following populations: elderly persons who may be prone to lithium toxicity (Himmelhock, Neil, May, Fuchs, & Licata, 1980), women (Kirov, 1998), and patients with a history of thyroid disease (Kusalic & Engelsmann, 1999). Lithium should be avoided in patients with renal disease or renal insufficiency because of lithium's increased risk for renal tubular damage (Gitlin, 1999), diabetes insipidis (Bendz & Aurel, 1999) and renal insufficiency and failure (Fenves, Emmett, & White, 1984). Kidney function can be checked and monitored with periodic serum creatinine levels (American Psychiatric Association, 2002a).

Lithium is FDA-approved for certain mental disorders even when the patient has cardiovascular disease. It should however be avoided for the non-FDA approved indication of PIA (Felthous, 2013) because of its association with atrioventricular block (Martin & Piascik, 1985), sinus bradycardia (Stecker, 1994), T-wave changes and ventricular irritability (Mitchell & MacKenzie, 1982). Lithium should be avoided where there is the possibility of drug-drug interaction with adverse results. Neurotoxicity is associated with co-administration of lithium and calcium channel blockers such as diltiazem and verapamil (Dubovsky, Franks & Allen, 1987; Finely, Warren & Peabody, 1995; Helmuth, Ljaljevic, Ramirez, & Meltzer, 1989; Wright & Jarrett, 1991). When prescribed together with angiotensin-converting enzyme inhibitors (i.e., antihypertensive agents such as captopril and lisinopril (DasGupta, Jefferson, Kobak, & Greist, 1992; Finley, O'brien, & Coleman, 1996), thiazide diuretics (Finley, Warren & Peabody, 1995), and onsteroidal anti-inflammatory agents such as ibuprofen and naproxen (Johnson, Seidman, & Day, 1993). If the patient must be prescribed a medicine from one of these categories, then lithium would not be the AIAA of choice (Felthous, 2013). In correctional settings but also in the community psychiatric and medical treatment can be compartmentalized. Therefore, it behooves all prescribers to know what other medication the patient is taking. Lithium can rise to toxic levels.

4.3 *Severity of Aggression*

Although more research is needed on the pharmacotherapy of subtypes of primary impulsive aggression, there is some evidence that Type 1 intermittent explosive disorder responds to fluoxetine whereas Type 2 may best be treated with an anticonvulsant AIAA or lithium. Type 1 IED is manifested by frequent but not physically destructive or injurious aggressive outbursts, a subtype of IED introduced in DSM-5 (American Psychiatric Association, 2013). Although also including Type 2 IED, Type 1 IED was the inclusion threshold for Coccaro's studies showing efficacy in the treatment of primary impulsive aggression (Coccaro, Lee, Kavoussi, 2009; Coccaro & Kavoussi, 1997). Compared with the other AIAAs, fluoxetine has the most favorable side effect profile and is most convenient to administer (Felthous & Standord, 2015), because unlike lithium and anticonvulsant AIAAs, regular blood draws for serum levels are not necessary (Felthous, 2013; Coccaro & Kavoussi, 1997).

If the aggressive episodes are serious, involving destruction of property and physical injury to other persons, it may be more prudent to turn directly toward lithium or an anticonvulsant AIAA (Felthous, 2015). The studies by Barratt and colleagues showed efficacy of phenytoin in treating PIA with consequentially severe rage outbursts (Barratt et al., 1997a, 1997). If one AIAA results in no improvement after adequate trial, the other may be worth a trial. Although not tested empirically fluoxetine and an anticonvulsant AIAA may be more effective than either alone, fluoxetine affecting serotonin availability in the frontal lobes (Coccaro et al., 2009), whereas the anticonvulsant AIAAs adjust the glutamate/GABA balance in the amygdalae (Stahl & Morrisette, 2014).

4.4 *Parsimony*

Efficiency is a virtue in prescribing any medication. Especially when prescribing an AIAA for PIA, an indication not approved by the FDA, the justification can be increased if there is a co-occurring disorder in need of treatment for which an AIAA is approved. An example of a disorder that commonly co-occurs with mental disorders including PIA is seizure disorder. This co-occurrence would disfavor the selection of lithium which is not an anticonvulsant. This principle of parsimony also applies to the selection of an anticonvulsant for treatment of a seizure disorder that is co-occurring with PIA. Levetiracetam would be a disfavored anticonvulsant because it has no beneficial effect on PIA

(Mattes, 2008). For co-occurring PIA and seizure disorder, the selection of an AIAA that offers this "two-for-one" advantage is limited to phenytoin, carbamazepine/oxcarbazepine, and valproate/divalproex (Felthous, 2015).

This principle of parsimony may justify treating a pregnant woman's PIA with an anticonvulsant, if the anticonvulsant is an AIAA, and the type and frequency of seizures do not permit withdrawal of the anticonvulsant before conception (Felthous, 2015). This is because the risk of harm to mother and fetus is greater than the teratogenic risk of the anticonvulsant AIAA (Lowenstein, 2013). In this case precautions can be taken to reduce the teratogenic risk to the fetus: mono-anticonvulsant therapy, lowest effective dose in the first trimester, prescription of folate and oral vitamin K during the last two weeks of pregnancy and injecting the infant with vitamin K intramuscularly at birth (Beghi & DiMascio, 1986).

All AIAAs except phenytoin have been FDA approved for treatment of a mental disorder. The presence of such a disorder affords an opportunity for prescribing one agent for two mental conditions, impulsive aggression and the disorder for which the agent is an FDA approved treatment: Fluoxetine for depression, obsessive-compulsive disorder, and bulimia nervosa (Physician's Desk Reference, 2012), valproate for mania (Physician's Desk Reference, 2012). Valproate/divalproex, carbamazepine and lithium are mood stabilizers that are also effective agents for bipolar I and II disorders, and so are ideal for the treatment of co-occurring impulsive aggression (Felthous, 2013).

Other conditions for which an AIAA may also be effective are: panic disorder (Michelson et al., 2001), posttraumatic stress disorder (van der Kolk et al., 1994), premenstrual dysphoric disorder (Menkes, Taghavi, Mason, & Howard, 1993; Perlstein et al., 1997; Steiner et al., 1995; Su et al., 1993; Su et al., 1997; Wood, Mortola, Chan, Moossazadeh, & Yen, 1992), premature ejaculation (Graziottin, Montorsi, & Graziottin, 1996) and pain associated with diabetic neuropathy (Max et al, 1992), fibromyalgia (Arnold et al., 2002; Goldenberg, Mayskiy, Mossey, Ruthazer, & Schmid, 1996) and possibly nightmare disorder (Felthous, 2013), for fluoxetine, epilepsy and migraine headaches for valproate/divalproex (Physician's Desk Reference, 2012); trigeminal neuralgia (Boes et al., 2008), partial and generalized tonic-clonic seizures (Trescher & Lesser, 2008), and neuropathic pain (Harati & Bosch, 2008) for carbamazepine; painful dysesthesias of Fabry's disease (angiokeratoma corpus diffusum) (Islam and Roach, 2008) and pain of glossopharyngeal neuralgia (Boes et al., 2008) by carbamazepine as well as by phenytoin; partial and generalized tonic-clonic seizures (Brodie & Dichter, 1966) and trigeminal neuralgia (Boes et al., 2008), for phenytoin; prophylactic treatment of cluster headaches (Boes et al., 2008, for lithium. In addition to its mood stabilizing effect, lithium also has a specific anti-suicide effect (Ahrens & Müller-Oerhinghauseir, 2001).

4.5 *Pharmacotherapy History*

Important in selecting any psychotropic agent for any mental disorder, but especially important is selecting an AIAA for primary impulsive aggression, a non-FDA approved condition, is obtaining a careful medication history. The purpose is to find if a particular AIAA has been used before and was associated with reduction in the impulsive aggression and with few to no side effects (Felthous & Stanford, 2015). The treating psychiatrist should bear in mind the possibility that an AIAA was previously prescribed for another indication such as bipolar disorder or seizure disorder. If from careful questioning it was shown to have resulted in reduced impulsive aggression, this would favor the agents selection.

4.6 *Affordability and Availability*

An important consideration is the selection of any medication for any condition is whether the patient can afford it and whether it will be available to the patient. These conditions must be addressed before selecting an AIAA. If an agent is not available once the patient is transferred back to a jail or a prison, it may not be administered. A medication that is not affordable or available to the patient after discharge from the hospital into the community, he will not be expected to continue to take it (Felthous, 2013).

5. Aggression Secondary to a Mental Disorder

Aggressive behavior that is symptomatic of a specific mental disorder may phenomenologically be primarily impulsive, primarily premeditated but with an illness-derived motivation (e.g., delusion), mixed or both. At any rate the first approach is to prescribe in order to treat the primary disorder, as secondary aggression typically improves along with other symptoms of the disorder (Felthous, 2015). Where the aggression does not improve, another strategy can be considered such as adding an AIAA, especially if the aggression, though secondary, is primarily impulsive. In some cases the co-occurrence of aggressive behavior can inform the selection of the agent for treatment of the primary mental disorder.

5.1 *Bipolar Disorder*

Manic episodes can be attended by exceptionally aggressive behaviors, including impulsive aggression that is secondary to mania (Felthous, 2013). In a study by Quanbeck and colleagues, most of those with bipolar disorders who were arrested were manic (74.2%) and/or psychotic (59%) at the time of their arrest (Quanbeck, Stone, Scott, McDermott, Altshuler & Frye, 2004). The risk of aggression can be increased with psychosis or substance use (Asnis, Kaplan, Hundorfean, & Saeed, 1997). Although serious violence with mania is rare, manic patients are often assaultive or threatening (Krakowski, Volavka, & Brizer, 1986). Especially when restrained or when limits are placed on their behavior, patients with mania commonly react with aggression (Tardiff & Sweillam, 1980). In Fazel's study of over 3,700 individuals diagnosed with bipolar disorder in comparison with controls and unaffected siblings, those with bipolar disorder had an increased rate of violent crime, but excessively violent crime we associated with substance us co-

morbidity (Fazel, Lichtenstein, Grann, Goodwin, and & Langstrom, 2010).

Some of the efficacious mood stabilizers are also efficacious AIAAs. The risk of assaultiveness subsides *pari passo* as the mania is brought under control. Hyperactivity and impulsivity of mania are reduced by both valproate and lithium (Swann, Bowden, Calabrese, Dilsaver, & Morris, 2002). Hostility appears to be attenuated more effectively with valproate (Bowden, 2004; Swan et al., 2002). If either is effective the clinician can change the mood stabilizer to carbamazepine or topiramate (Moeller & Swann, 2007). In contrast to the anticonvulsants divalproex/valproate and carbamazepine, lithium although an effective AIAA for primary impulsive aggression (Barratt et al., 1997a, 1997b), phenytoin is not approved as an anti-mania agent. If aggression is not improved by the mood stabilizer alone risperidone may be added (Moeller & Swann, 2007). The American Psychiatric Association guidelines recommend the combination of an antipsychotic and a mood stabilizer such as lithium or carbamazepine as more effective in the treatment of severe aggression than either such agent alone (APA, 2002).

5.2 *Schizophrenia and Psychotic Disorders*

Antipsychotic agents are generally effective in the treatment of psychosis and schizophrenia, with quelling of any accompanying aggressive behavior. Aggressive behavior is most likely to occur with schizophrenia when the patient is actively psychotic (Keck, Strakowski, & McElroy, 2000). Although aggressive behavior can result from the psychotic symptoms themselves such as delusions (Taylor, 1985; Taylor et al., 1994), much of the aggressive behavior in schizophrenia can be described as impulsive (Felthous, 2008; Felthous et al., 2009). Atypical antipsychotics have been shown to reduce the aggressive behavior of psychotic disorders (Keck et al., 200; Nasralla & Tandon, 2002), more so even than typical antipsychotics (Chengappa, Goldstein, Greenwald, John & Levine, 2003; Citrome et al., 2001; Lieberman, 2004).

Several of the studies demonstrating superiority of an atypical antipsychotic in reducing hostility and aggression found favorable results with quetiapine (Chengappa et al., 2003; Lieberman, 2004; Nasrallah & Tandon, 2002). Before selecting quetiapine however, the clinician must also consider its singular reputation for abuse with an appreciation of the widespread substance abuse among offender populations (Eder, 2008; Pina, 2007).

An agent with demonstrated efficacy in reducing hostility in schizophrenic patients is olanzapine, significantly superior to haloperidol, amisulpride and quetiapine (Volavka, Czobor, & Derks, et al., 2011) and to perphenazine and quetiapine in another study (Volavka, Czobor, Citrome, & Van Dorn, 2014). The multicenter CATIE study showed olanzapine to be significantly more efficacious than perphenazine, quetiapine, risperidone, and ziprasidone in reducing hostility as assessed by the PANSS Hostility items (Volavka, Czobor, Citrome, and Van Dorn, 2016). The PANSS Hostility item, which may include overt aggression, is used as a proxy measure of aggression (Volovka, 2002): A meta-analysis of risk factors in persons with psychosis estimated that higher hostility scores and hostility during the study period were significantly associated with increased risk of violence (Witt, van Dorn, & Fazel, 2013).

Prior to recent research favoring olanzapine, risperidone was emerging as an especially effective antipsychotic agent in controlling aggression in patients with schizophrenia (Aleman & Kahn, 2001; Chengappa et al., 2000; Moeller & Swann, 2007). Like other atypical antipsychotics, risperidone was thought to reduce aggression by improving executive functioning, thought processing as well as controlling psychotic thoughts and perceptions that result in behavioral dyscontrol. If an atypical is ineffective, a typical antipsychotic can be tried (Felthous, 2013). For schizophrenia associated with violent behavior that is resistant to treatment, Morrisette and Stahl (2016) and Meyer (2016) recommend high-dose monotherapy of the selected antipsychotic using plasma levels rather than dosages for titration. Risperidone's D_2 occupancy, for example, can be estimated based on risperidone's serum concentration (Uchida, Takeuchi, & Graff-Guerrero et al., 2011). The usual dose range is 10-20 mg/day (Morrissette & Stahl, 2016), and the recommended plasma level is within the range 20-60 mg (Kiemke, Baumann, & Bergeman et al., 2011). The FDA approves up to 80 mg/day and very high doses are usually not tolerated (Morrisette & Stahl, 2016). For olanzapine the minimum threshold for response is 23.2 mg/ml (Perry, Lund, Sanger and Beasley, 2001). An estimated 70 mg ng/ml is needed for 80% D_2 occupancy (Uchida et al., 2011). The usual dose range is 10-20 mg./day, and recommended plasma levels are 20-80 ng/ml (Hiemke et al., 2011). In some forensic settings the dose administered is as high as 90 mg/day (Morrisette & Stahl, 2016). A treatment-compliance advantage for both risperidone and olanzapine is that they can be administered via a long acting depot formulations which can be supplemented with the oral formulation (Morrisette & Stahl, 2016). Clozapine is not the first choice because of its adverse side effect profile including the risk of potentially lethal agranulocytosis as well as the need for patient cooperation with multiple blood draws. However, where other agents have failed clozapine can often reduce psychotic symptoms as well as the schizophrenic patient's impulsively aggressive behavior (Buckley, Bartell, Donenwirth, Lee, Torigoe, & Schulz, 1995; Fava, 1997; Glazer & Dickson, 1998; Krakowski, Czobor, Citrome, Bark & Cooper, 2006; Moeller & Swann, 2007; Rabinowitz, Avnon, & Rosenberg, 1996). Even after controlling for sedation, clozapine directly reduces long-term violence in patients with schizophrenia (Chiles, Davidson, & McBride, 1994; Citrome et al., 2001). In some cases optimal effects are achieved by combining clozapine with one or more other antipsychotic agents (Hotham et al., 2016; Meyer, 2016).

No doubt mood stabilizers are often used in combinations with antipsychotic agents to control mood swings in schizoaffective disorder, but also to control aggressive behavior associated with schizophrenia. One study showed one third of schizophrenic patients were prescribed both an antipsychotic and a mood stabilizer (Citrome, Levine, & Allingham, 2000). A mood stabilizer that is commonly co-prescribed with an antipsychotic in the treatment of schizophrenia is valproate (Bowden, 2004), and studies show this can result in improved global functioning (Bogan, Brown, & Suppes, 2000; Casey et al., 2003; Wassef et al., 2000). Even

if aggressive behavior is not directly tested, one might reasonably assume that increased global functioning includes diminished aggressive behavior (Felthous, 2013). Some reports indicate that valproate is associated with reduced plasma levels of clozapine (Longo & Salzman, 1995) and olanzapine (Haslemo, Olsen, Lunde & Moldar, 2012). This raises the possibility of subtherapeutic levels of an antipsychotic agent when valproate is co-administered, unless the dose of the antipsychotic is increased. Dose and colleagues found that valproate combined with haloperidol reduced "hostile belligerence" in the treatment of schizophrenic psychosis (Dose, Hellweg, Yassouridis, Theison, & Einrich, 1998).

Carbamazepine has been used to treat psychotic and behavioral disorders (De Vogelaer, 1981), and it has been found to diminish aggressive behavior when combined with antipsychotic medication (Okuma et al., 1989). Carbamazepine may be an even more potent inducer of antipsychotic metabolism, requiring a higher dose of the antipsychotic and plasma antipsychotic levels (Meyer, 2016).

A third mood stabilizer which is also an AIAA has been shown to reduce aggressive behavior in schizophrenia, when prescribed in combination with an antipsychotic, in particular with clozapine (Bender et al., 2004). Of the three lithium is least likely to induce antipsychotic metabolism (Meyer, 2016). However its efficacy with other antipsychotics is not strongly (?) supported by the literature (Collins et al., 1991; Wilson, 1993).

6. Traumatic Brain Injury

Several studies have indicated an association between traumatic brain injury and criminal or violent conduct (Grafman et al., 1996; Sarapata et al., 1998; Freedman & Hemenway, 2000), the classic example being Phineas Gage (Harlow, 1848). In one study 33.7% of patients with TBI showed chronic aggressive behavior (Tateno, Jorge & Robinson, 2003).

The aggression associated with traumatic brain injury has been treated with beta adrenergic blockers (Greendyke & Kanter, 1986; Greendyke, Kanter, Shuster, Verstreate, & Wootton, 1986, 1989), the evidence provided by Greendyke and colleagues consisting of double-blind, placebo-controlled studies (Newman & Tardiff, 2017). In 1977 Elliot first described a favorable response to the treatment of TBI patients with rage outbursts who were prescribed propranolol. Especially, because propranolol and other beta-blockers are not FDA approved for treating TBI associated aggression, "two-for-one" indications may be considered (Felthous, 2013). Co-occurring conditions that may respond to propranolol providing further justification for its use in TBI include migraine headaches (Boes et al., 2008; Silberstein, 2000), tremor from multiple sclerosis (Blublin & Miller, 2008), neuroleptic-induced akathisia (Kulik & Wilbur, 1983; Lipinski, Zubenko, Barriera, & Cohen, 1983), restless leg syndrome (Ekbom, 1965), and familial essential tremor (Jankovic & Shannon, 2008). Cardiovascular conditions for which beta-blockers are FDA approved are ventricular tachycardia, supraventricular arrhythmias, angina from coronary arteriosclerosis, and hypertension (Jankovic & Shannon, 2008).

As with other agents not approved by the FDA for treatment of clinical aggression, the prescribing physician must be especially aware of the risks associated with beta-blockers (Felthous, 2013). Asthma, congestive heart failure, diabetes and third-degree atrioventricular block are contraindications. Common side effects are bradycardia, depression, diarrhea, fatigue, impotence, nausea and rash (Jankovic & Shannon, 2008). Neuropsychiatric side effects include ataxia, behavioral changes, confusion, and respiratory depression (Lublin, & Miller, 2003). Other side effects that can warrant discontinuation are hypotension, insomnia and nightmares (Boes et al., 2008).

Side effects such as bradycardia and hypotension were causes for discontinuations in early studies wherein doses of propranolol were higher than those commonly used to treat hypertension (Greendyke, Berkner, Webster, & Gulya, 1989). A recent study provided evidence for anti-aggressive efficacy with a lower dose; pindolal was prescribed at 3 mg. three times a day (Caspi et al., 2001).

The generic form of pindolal lends itself to easy titration. At higher doses pindolol shows partial agonism of intrinsic sympathomimetic activity (ISA) resulting in less bradiocardia and hypotension than occurs with propranolol (Newman & Tardiff, 2017).

Certain mood stabilizers which have demonstrated efficacy in the treatment of primary impulsive aggression, have also been shown to reduce aggression of TBI. Several studies support the use of carbamazepine (Azouvi, Jokic, Attal, Denys, Markabi, & Bussel, 1999; Geracioti, 1994; Horne & Lindley, 1995; Wroblewski, Joseph, Kupfer, & Kalliel, 1997). Lithium has been used where the aggression did not subside with haloperidol or propranolol (Haas & Cope, 1985), but lower doses of lithium are recommended for TBI associated aggression because of the increased sensitivity of TBI patients to lithium's side effects (Hornstein & Seliger, 1989). Because TBI associated aggression is phenomenologically impulsive, the question arises as to whether other AIAA would be as efficacious, but have not yet been subjected to drug trials in this population.

Conclusions

An important aspect of providing mental health services to offenders is the safe and effective pharmacotherapy of clinical aggression. Aggressive behavior that can subside with pharmacotherapy is primary impulsive aggression and aggression that is secondary to certain other mental disorders. Because no medication is FDA approved to treat impulsive aggression, the clinicians must give special attention to principles of selecting the most beneficial and effective AIAA with the least risk for the individual patient. Of the various mental disorders with the possibility of secondary aggression, three of the most common and serious disorders are addressed here – schizophrenia, bipolar disorder and traumatic brain injury — with emphasis on treating the disorder as well as the disorder's symptomatic aggression.

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