SERENICS: ANTI-AGGRESSION DRUGS THROUGHOUT HISTORY

Willem M.A. Verhoeven and Siegfried Tuinier

Abstract

Object: In this paper an overview is presented of the enduring efforts of physicians to control aggressive and disinhibited behaviors irrespective of the nosological context. Compounds that are thought to have a specific antiaggressive effect are called serenics.

Method: First, a selective review of the historical concepts is outlined together with the treatment modalities. Second, the pharmacological approaches are described that have been developed since the introduction of psychotropics.

Results: From ancients times on several herbal sedatives and containment strategies have been used to control manifestations of aggression. In the second half of the past century, all psychotropics have been advanced as a potential treatment. The results, however, are only aspecific. During the past decade, animal experiments have shown that systemic administration of specific serotonin receptor antagonists may exert behavioral specific effects.

Conclusions: So far no specific pharmacological treatment is available for aggressive behaviors. Modern research suggests that aggressive behavior should be studied as a separate functional disorder across diagnostic boundaries.

Key words: Aggression – History – Psychotropics Serenics

Declaration of interest: None

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Introduction

Control of aggressive or impulsive behaviours has always been a major concern of physicians when confronted with mentally ill patients. Reports on behavioural dyscontrol and its potential remedies can be found in handwritten and early printed documents that all witness the biological orientation of medicine. The Hippocratic and later ancient medical writers praised black hellebore (*Helleborus niger*) for excitation. Other sedatives commonly used were poppy seeds, mandrake and belladonna alkaloids like hyoscine. Jiménez-Olivares (1978) lists pre-Columbian 'psychotropic drugs' of which several were applied for the control of agitated behaviour. No essential changes in the pharmacotherapeutic armamentarium are noticeable until the sixteenth century (Ackerknecht 1979). The pharmacological properties of many of the ancient drugs are difficult to identify since they were but one facet of a total treatment program (Feldman 1965) and nosology was totally influenced by the Galenean humoral theories. The first compilations of knowledge about biological medicine are presented in the early Renaissance encyclopaedias of Albertus Magnus, Alexander Neckam, Thomas Cantimpré, Vincentius de Beauvais and especially Bartolomaeus Anglicus. The latter's *de proprietatibus rerum* was immensely popular throughout the seventeenth century (Jansen-Sieben 1994). An example of a treatment plan in wild mental patients from Bartolomaeus Anglicus is: "*The diete shall be ful scarse, as crommes of breade-whiche muste many tymes be wette in weater. The medycyne is-that in the begynnynge the pacyentes heed be shaven, and washed in luke warm vynegre, and that he be well kepte or bounde in a darke place. In the begynnynge of medycine he shall be let bloudde in a veyne of the foreheed, and blede as moche as woll fyll an egge shelle. Afore all thynge (if vertue and age*

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suffryth) he shall bleded in the heede veyne. By medycyne dygestyon shall be procurid-and redde Colera quenched" (Hunter and Macalpine 1964). In this era the indications for specific pharmacological treatment are generally not specified but some can be found in the *Liber de simplici medicina* and the *Antidotarium Nicolai* (Goltz 1976, Braekman and Keil 1971).

Several doctors like Felix Platter (1536-1614) in Switserland published their case histories of patients including remedies, the so called *observationes*. One of them, called Petrus Forestus (Pieter van Foreest 1522-1597) from The Netherlands reported about psychiatric illness and he used physical restraints and an ointment containing poppy seeds and opium thebaicum for sedation. The transdermal resorption of his opiates was confirmed centuries later (Kutzer 1995).

In early modern times mentally ill patients were either kept at home or admitted to a hospice for poor people or were sometimes kept in prison (Magherini and Biotti 1998). In case of disorganised or aggressive behaviour, however, patients in the low countries of Europe were institutionalised in the monasteries of the cell-brothers from the *Congregatio Fratrum Alexianorum Cellitorum*, who also cared for the plague victims (Kauffman 1976). The physician was consulted after the priest and the folk healer for the simple reason that he was not able to cure. In the following centuries, opium remained one of the main sedative drugs and from 1696 to 1793 a few monographs were published about its beneficial effects (Burchard 1967, Siegel and Hirschman 1983). In 1826, Charvet was the first who experimentally evaluated the effects of opium in various animals as well as in patients. As a consequence of social changes in the 18th century, the mere seclusion of mentally ill patients was less tolerated (Elias 1982) and a great impetus was given to the search for effective tranquilizing compounds.

Putative ancient serenic agents

Herbal sedatives

For centuries herbal sedatives, whether or not effective, have been prescribed by doctors for calmative purposes. Well known examples are *Humulus lupulus* (hop) which is related to hemp, *Valeriana officinalis* (valerian), *Cannabis sativa* (hemp), *Lavendula officinalis* (lavender) and *Passiflora incarnata* (passion flower). These herbal sedatives appeared in the recipes of the fifteenth and sixteenth century (Platter 1614, Bikker 1765). Some of them are still used as over the counter medications.

Alkaloids

Preparations of belladona have been prescribed by physicians for many centuries for several indications. The alkaloid hyocine, especially its L-isomer scopolamine, is found chiefly in *hyoscyamus niger (Henbane)*. D,L-hyocine, atropine, is also found in *Datura Stramonium*. During the time of the Roman Empire and the Middle Ages, hyocine was frequently prescribed since it induces depression of the central nervous system resulting in sedation. The alkaloid mandrake from the Mediterranean plant *Mandragora officinalis* was used for its sedative and hypnotic properties (Bowman 1979). Atropine and the other alkaloids were isolated in the first half of the 19th century. Until the beginning of the last century, alkaloids like scopolamine were frequently used in combination with morphine as treatment modalities for excitement and agitation in psychiatry. They were among the most reliable and effective treatments for the rapid control of behaviour (Ban 2001).

Opiates

That opium, derived from the *Papaver somniferum*, relieves both pain and anxiety and promotes sleep and a feeling of well being, was already known to the Babylonians 4000 years B.C. The Greeks and Romans were well aware of its sedative properties. At the end of the Middle Ages Paracelsus introduced the name *laudanum* for preparations containing it. Later pharmacists referred to it as *Laudanun liquidum Sydenhami*. It was not before the nineteenth century that the active ingredients of opium were isolated. By the middle of the nineteenth century pure alkaloids took the place of opium in medicinal use (Holzer and Lembeck 1983), although, for instance in French psychiatry, *laudanum* continued to be used for a variety of indications till the beginning of the last century (Sueur and Hodgkiss 1995). Several combinations of *laudanum* and other sedatives were given to preserve tranquillity in the French psychiatric hospitals (Dumesnil and Laillier 1868, Sueur 1997). In that era *laudanum* was considered to be the most appropriate compound to control aggressive behaviour. In 1868 Demesnil and Lailler stated: *'C'est là, en effect, qu'il trouve les agents les plus propres à calmer l'excitation morbide si fréquente chez les aliénés; c'est là qu'il rencontre l'opium, l'une des substances les plus indispensables dans l'art de guérir'*.

There are good indications that substances like hyocine and opiates were used from about 1840 to deliver what amounted to sleep therapy in the beginning of the last century. The combination scopolamine/morphine was prescribed for the acute control of aggression and agitation untill the seventies of the past century.

Developments from 1850-1950

Chloral hydrate, paraldehyde and bromides

In 1862 the German chemist Justus Liebig discovered chloral hydrate that was introduced in clinical practice in 1869 by Oscar Liebreich because of its sedative properties. Chloral hydrate was used very often from the end of the 19th century to the middle of the 20th century (Gauillard et al. 2002). In 1886 a second aldehyde, paraldehyde was synthesized and introduced in the clinic.

Since the mid fifties of the 19th century, bromides were widely prescribed for the treatment of epilepsy and concomitant insanity. For agitation sodium bromide

was popular (Sueur 1997, Lund 1997).

Chloral hydrate was prescribed both as a sedative and a hypnotic and paraldehyde was in later years used for the treatment of alcohol withdrawal and bromides were prescribed for sedation and the the treatment of epilepsy (Hollister 1983). Chloral hydrate is still available and up till now incidentally used for sedation.

Barbiturates and non-barbiturate hypnotics

Barbiturates have been known since the latter part of the 19th century and barbital (Veronal) was the first barbiturate introduced into clinical pratice. Barbiturates replaced the bromides and they were widely precribed as sedatives. The barbiturates were classified according to their span of action and phenobarbital was used in case of agitation and anxiety (Hollister 1983). The hegemony of the barbiturates (1903-1945) was eventually threatened by the gradual recognition of their acute and chronic toxicity and their abuse potential. During the search for non-barbiturate hypnotics, meprobamate was introduced in the mid fifties of the last century. From animal experiments it became clear that this compound possessed anti-aggressive properties (Berger 1956) and it was introduced for the treatment of anxiety (Berger 1962). At the same time glutethimide was developed as a non-barbiturate hypnotic agent. Barbiturates and meprobamate were received with great enthousiasm as potential tools to support a 'no restrain policy' in clinical psychiatry. From the mid fifties to 1961, meprobamate enjoyed a vast popularity, but with the advent of the benzodiazepines, it quickly lapsed into obscurity.

Lithium

Although in the Greek, Roman and Arabic sources no specific reference to lithium is made, the use of alkaline waters for the treatment of mental illness called mania has been described since Caelius Aurelianus in the fifth century. In a section on the treatment of 'mania' he wrote *"utendum quoque naturalibus aquis, ut sunt nitrosae"* (use should also be made of natural waters, such as alkaline springs). In the 19th century a multitude of lithium products, including mineral waters, salts, tablets and even Lithia beer was sold for medicinal purposes. On the instructions for use it was mentioned that the medication was safe and effective for the treatment of nervous disorders in all their forms. Almost all the bottled 'curative' waters marketed at present, were at one time advertised for the high lithium content. It was not until 1855 that lithium was isolated by Bunsen and Matthiessen (Kline 1969). In the second half of the 19th century lithium was systematically applied by Carl Lange (1834-1900) in patients with recurrent depression (Felber 1987). In the first decades of the last century, lithium was rediscovered as a treatment for hyperactive and excited states, not necessarily related to mania (Cade 1949, Despinoy and de Romeuf 1951)

Non-pharmacological interventions for sedation

In the late nineteenth and the early twentieth century physical restraint and somatic remedies were regularly used in the control of aggression and other disinhibited behaviours. Because drugs and physical restraint had a bad reputation as treatment methods, other forms of treatment were developed that were believed to be more efficacious (Von Keyserlingk 1976, Braslow 1994).

In general, containment strategies to control violent or aggressive behavior are not supported by evidence from controlled studies (Muralidharan and Fenton 2006).

Hydrotherapy

Although medicinal powers of water had been known for centuries, by the end of the 19th century physicians had introduced hydrotherapy as a legitimate medical technology for the treatment of violent and excited patients (Winslow 1896). The most common methods consisted of the so-called wet pack, the continuous bath, the douche and the spray. It was thought that the efficacy of hydrotherapy resided in its biological effect (Foster 1899, Jackson 1915).

Fever therapy

Hyperthermia was believed to be a more specific form of treatment for a number of disorders including violence and it could be induced by either injection of a sodium salt or inoculation with malaria and tuberculin.

Insulin coma therapy

This form of treatment was indicated for acute excitement and other conditions with severe psychomotor agitation. The result of hypoglycemia was tranquillity for some hours (Slotopolsky 1931).

As with many other treatments, hydrotherapy, fever therapy and insulin coma therapy were gradually abandoned in the first half of the 20th century because of lack of effect and unwanted side effects.

Before the psychotropics

As outlined above, the history of 'serenics', compounds aimed at the induction of tranquillity or lack of agitation, was until the seventeenth century dominated by the Galenian concept which consisted of restoration of the balance between the four primary qualities (*humores*). In fact, this approach can be considered as an early example of syndromal in stead of nosological thinking. Urban developments necessitated the foundation of institutions such as early hospitals that later on developed into mental hospitals in which restraint was the predominant treatment of unmanageable behaviours. In the 19th century restraint became less accepted and attempts were made to discover drugs with sedative properties. Several compounds were discovered or synthesized that showed an aspecific effect in a variety of disorders accompanied by disinhibited behaviours. This culminated in the wide spread use of lithium, barbiturates and the barbiturate

substitute meprobamate for among others behavioural control. Treatment was more symptom oriented and targeted on symptoms that were hardly differentiated like anxiety, aggression, excitement and irritability.

The introduction of chlorpromazine in the early fifties of the 20th century led to a separation between the so called major and minor tranquilizers that were all, as the name suggests, aimed at tranquillity. The need for anti-aggression drugs has been throughout history a dominant theme in medicine.

Anti-agressive Psychotropics

Several psychotropic agents were developed either because of a potential antiaggressive effect or after introduction clinically used as such. From 1883 on phenothiazine and derivates were synthesized. It lasted, however, until the 1930s that a clinical use was found for one of the members of this group, the antihistamine promethazine. This compound was used by the French surgeon and physiologist Henri Laborit who asked the manufacturer for a drug with central effects stronger than those of promethazine. This led to the synthesis of chlorpromazine that was originally used in cases of agitation and exitement (Hamon et al. 1952). Delay and Deniker (1952) were the first to describe the antipsychotic effect. The same holds for the first butyrofenone derivate haloperidol that originated from the research into morphinomimetic drugs and that was marketed as an antipsychotic in 1959. Concerning the benzodiazepines, which were originally developed by Sternbach in the mid-1930s, it was noticed that these compounds had an impressive 'taming' effect in animals with spontaneous or experimentally induced aggression (Randall 1960). The first benzodiazepine, known as methaminodiazepoxide, later named chlordiazepoxide, was reported to possess specific anxiolytic properties (Harris 1960).

Since the 1960s all available antipsychotics have been used in the symptomatic treatment of aggression in patients with all kind of psychiatric disorders or aggressive behaviour as such. Most of the at present marketed antipsychotics have an additional indication for the treatment of excitement and agitation. Apart from the antipsychotic drugs, several other compounds have been or are in use to alleviate behavioural disinhibition.

Antipsychotics

As far as positive results are reported, they deal with sedation, motor inhibition or reduction of aggression secondary to anxiety or psychosis (Brylewski and Duggan 2004, Volavka et al. 2006, Nosè et al. 2006). It should be stressed, however, that antipsychotics, especially the conventional neuroleptics, may provoke aggressive behaviour via the induction of akathisia, even after they are withdrawn (Keckich 1978, Gualtieri 2002) or they can lead to so called behavioural toxicity characterised by a deterioration of mental state (Gualtieri 1991). Whether the modern atypical antipsychotics or clozapine do reduce impulsiveness and aggressiveness independent of their antipsychotic action is still questionable. The reports so far deal with case or chart reviews only (De Leon 1994, Spivak et al. 1997, Volavka 1999, Briken et al. 2002) or with prospective obervational studies (Bitter et al. 2005).

Although antipsychotics possess antiaggressive properties in the acute phase of treatment, the development of tolerance is clearly demonstrated in animal experiments (Garmendia et al. 1991, Mos et al. 1996). This topic is generally not addressed in human studies but clinically very relevant. Finally, extensive preclinical studies have demonstrated that antipsychotics with a high affinity for dopamine D_2 receptors are not specific antiaggressive compounds (De Almeida et al. 2005).

Lithium

Since the early seventies several studies have been performed with lithium for aggressive behaviour in a variety of patient populations (Sheard 1971, Tupin et al., 1973, Sheard et al. 1976). The results of these studies, however, have to be interpreted with caution because of several methodological problems. The last two decades no relevant studies have been published and in all evidential support is lacking for the efficacy of lithium on aggressive behavior (Volavka et al. 2006).

Anticonvulsants

For a long time carbamazepine has been advocated for behavioural control, although only one placebo-controlled study is published that demonstrates, however, no effect on aggressive behaviour (Cueva et al. 1996). Some beneficial effects of valproic acid have been reported on aspects of behavioural disinhibition like irritability and impulsivity (Davis et al. 2000, Hollander et al. 2003, Steiner et al. 2003, Golden et al. 2006). One study reports an antiaggressive effect of topiramate in intellectually disabled patients (Janowsky et al. 2003). Caution is necessary with respect to topiramate since this anticonvulsant is demonstrated to provoke aggressive behaviour as well (Mula and Trimble 2003). The same holds for levetiracetam (Dinkelacker et al. 2003).

Antidepressants

A variety of studies deal with antidepressants (TCA's and SSRI's) and the putative antiaggressive effects of these compounds (Soloff 1994, Rinne et al. 2002). Sofar a very limited number of controlled studies have been published in aggressive behaviours per se. The spurious beneficial effects concern accompanying symptoms, but not aggression, in personality disordered patients (Tuinier and Verhoeven 1995, Tuinier et al. 1996, Nosè et al. 2006). Whether impulsive self-aggression can be provoked by SSRI's is still under debate (Walsh and Dinan 2001).

Other compounds

Already in the mid sixties it was observed that

betablocking agents reduce somatic symptoms of anxiety. Over the past decades a limited number of studies adress the effect of betablockers in patients with aggression and impulsivity secondary to an organic brain disorders (Ratey and Lindem 1991, Thibaut and Colonna 1993, Rudrich 1996). The paucity of publications in recent years warrants scepticism about the clinical value of these compounds.

Based on the hypothesis that especially 5-HT_1 receptors are involved in the regulation of impulse control (De Boer et al. 1999, Pruus et al. 2000), 5-HT_{1a} agonists like *buspirone* have been investigated. From preclinical studies it was predicted that these compounds should be effective in those patients who exhibit impaired coping with stress and hyperarousal resulting in uncontrolled behaviours. The clinical results, however, are so far disappointing (Verhoeven and Tuinier 1996, 1999).

In conclusion, history so far demonstrates that virtually all compounds with psychotropic properties have been used in the treatment of aggressive behaviour. They were welcomed with initial enthousiasm and the 'effect' gradually faded away.

Serenics

In the aftermath of the second World War and the Cold War and social unrest, researchers discussed how their knowlegde, skills and research efforts could be applied to the problems of individual and collective violence. This initiative resulted, in 1972, in the foundation by preclinical researchers of the International Society for Research on Aggression (ISRA). This type of research was mainly confined to the preclinical level and the animal models since psychiatry was absorbed in the development of a new taxonomy in which aggression and violence were not included as a separate functional disturbance.

The development of drugs, specifically aimed at the reduction of pathological destructive behaviour in psychiatric patients, was started halfway through the seventies of the past century. The compounds used until then, had no specific effects upon behaviour or were associated with significant adverse effects or both. This prompted the research for drugs that specifically inhibit destructive behaviours without significant behavioural, psychiatric or somatic side effects. These compounds were tentativelly called 'serenics' which refers to tranquillity or lack of agitation. To this end a set of animal models was developed which would be functionally feasible to screen a large number of candidate drugs. To describe the behavioural profile of a drug an ethological screening procedure was constructed based on extensive observation and recording of the ongoing behavioural items such as offense, defense, social interest, flight, exploration and self care. Using this model it was possible to distinguish specific antiaggressive drugs from none, or less specific drugs. Two compounds, the phenylpiperazine analogues fluprazine and eltoprazine with a 5-HT_{1b} respectively 5-$HT_{1a,b,c}$ agonistic action, appeared to reduce aggression while leaving social behaviour and exploration unaffected and they were further screened in other animal models. The development of fluprazine was terminated because of toxic problems in animals. Eltoprazine showed a very specific inhibition of the offensive components of agonistic interactions without material effects on flight, defensive and social capabilities (Olivier et al. 1990).

Subsequently, another 5-HT_{1a} agonist, flesinoxan, and the 5-$_{HT1a,b,c}$ agonist eltoprazine have been investigated in human studies. Only two with flesinoxan were published, demonstrating either a slight reduction of depression (Grof et al. 1993) or a dose related enhancement of anxiety in patients with panic disorder (Van Vliet et al. 1996). With eltoprazine two open studies (Tiihonen et al. 1993, Tuinier et al. 1995) and one double-blind placebo-controlled study were performed in mentally handicapped patients with aggressive behaviour (De Koning et al. 1994). Only a temporary effect on aggressive incidents was reported, while in higher doses eltoprazine induced sleep disturbances and hyperactivity. One study was brought to a premature closure because of psychotic deterioration (Moriarty et al. 1994). The further development of these compounds was terminated soon afterwards.

About the same time it became clear from animal data that the group of phenylpiperazines, including m-chlorophenylpiperazine (MCPP), show psychostimulant and anxiogenic-like effects (Benton et al. 1983, Griebel et al. 1990, Rodgers et al. 1992) that account for the side effects in human studies. Moreover, MCCP as well as buspirone have been reported to posses propsychotic and anxiogenic effects in several patient groups (Soni and Weintraub 1992, Krystal et al. 1993).

Thus, the 'serenics' with a putative selective antiagonistic profile appeared not to be selective at all and the effect depends on specific animal models and species used as well as on the sex of the animal. Furthermore an anxiogenic effect underlies the modulation of behaviour (Blanchard et al. 1985, Parmigiani et al. 1989, Griebel et al. 1990).

Although the proposed animal models to elucidate potential antiaggressive characteristics of drugs are very elegant because of its ethological approach, this line of research is predestined to fail in view of the premise that models of normal animal behaviour can be extrapolated to complex human behaviours in patients with a great variety of pathological conditions. The currently used animal models to study aggression are not adequate since they focus on adaptive forms of aggressive behavior. Therefore, preclinical investigators proposed to study models of escalated or excessive levels of aggressive behavior that exceed the normal social codes (De Almeida et al. 2005, Haller and Kruk 2006). Animal experiments have shown that systemic administration of specific 5-HT_{1a} or $_{1b}$ agonistic compounds like alnespirone exert behavioral specific effects (De Boer and Koolhaas 2005).

In humans, the study of the pharmacology of aggression is extremely difficult because of the many methodological problems that arise in the design of appropriate clinical trials. These include: inprecise definitions of aggression, difficulties in the measurements of outcome, the relative rarity of aggressive events, bias in the selection of patients for study, inadequate and inappropriate control groups and inattention to comorbidities and concomitant

medications in analyzing results (Volavka and Citrome 1999).

Future directions

The development of psychotropics targeted at discrete behaviours or functional disturbances is promising but biased by the premise that aggression is a unitary concept. Language is, however, somewhat misleading because a great variety of disturbing or noxious behaviours are subsummed under the heading aggression. Even if a biologically relevant taxonomy of aggressive behaviour in humans would be feasable, a simple connection with a biological parameter like a receptor or a neurotransmitter is highly unlikely (Antelman and Chiodo 1984). In addition, it should be stressed that the activation of relevant biological systems depends on earlier experiences with the particular behaviour (Antelman et al. 1997). From preclinical research it has become clear that the neural circuits involved in many types of human and animal aggression, comprise multiple neurotransmission systems and receptor subtypes (Miczek et al. 1994, 2002; De Almeida et al. 2005).

Since the testing of serenics in daily life is virtually impossible, there is an urgent need for laboratory procedures that measure aggressive responding and impulsivity. Several instruments have been developed such as the Taylor Aggression Paradigm, the Point Subtraction Aggression Paradigm, the Continuous Performance Test and several frontal tasks (Giancola et al. 2003, Cherek et al. 2004). Although certain dimensions of aggressive behaviour can be measured with these procedures, their external validity has yet to be demonstrated. A more promising vantage point eminates from the so called MATRIX initiative that is aimed to stimulate the development of new drugs not for disorders per se like schizophrenia, but for cognitive functional impairments (Green 2007). This implies a new pathway for drug approval which may be also relevant for the study and the development of serenics. Such compounds may be targeted at the enhancement of the inhibitory function of the prefrontal cortex of which the functional relevance is elegantly described by Barkly (2001).

In conclusion, since aggressive behaviour forms a great social burden for which clinicians prescribe all kinds of drugs with or without good reason, there is an urgent need for research into compounds that affect aggressive behaviour selectively irrespective of the nosological context. This implicates pharmacological research into functional disturbances instead of ill defined diseases.

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