The Role of Serotonin in the Future of Forensic Psychiatry

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The role of serotonin in understanding suicidality, violence, impulse disorders, and paraphilias is described and the current state of our knowledge is reviewed. Clinical research in these areas will provide new understanding of behavior that leads to violations of the law. Forensic psychiatrists need to be more aware of these developments, and they must recognize that the uniqueness of their specialty lies in its clinical and research perspectives.

The story of serotonin probably begins with the identification and the synthesis of 5-hydroxytryptamine (5-HT) in 1953. It was originally identified as a serum vasococontractor released by platelets during the clotting of blood and was named serotonin by Rapport, Green, and Page. By 1953 it was noted that serotonin could be found in platelets, the gastrointestinal system, and the brain. Sjoerdsma and Palfreyman report that early researchers were obsessed with the extraction of the substance and worked to extract it from the serum of almost 2,000 pounds of beef blood, 60,000 pounds of octopus salivary glands, and more than 1,000 amphibian skins. The breakdown of all of this biological tissue resulted in a few crystals of serotonin. They also make the point that the present day molecular biologists are similarly obsessed with the identification of various serotonin receptors. The period from 1953 to 1970 is described by Sjoerdsma and Palfreyman as "The Renaissance." A lot of work was done in the area of serotonin studies, particularly in relation to the role of serotonin in hypertension. The first clinical application of serotonin was the discovery of its role in carcinoid syndrome. During this time period the role of serotonin in psychiatric disorders was questioned because of the action of lysergic acid diethylamide (LSD), a serotonin antagonist. There was also a discovery that reserpine depleted serotonin in the brain, whereas monoamine oxidase inhibitors increased serotonin content. Another important development was the synthesis of parachlorophenylalanine, which inhibited the synthesis of serotonin at the step of tryptophan hydroxylase.

During the 1970s there was not much development in the field, but there were various suggestions by several authors that serotonin precursors 1-tryptophan and 5-hydroxytryptophan were antidepressants.
Europeans were especially strong in supporting the role of serotonin in depression, whereas in the United States, the catecholamine hypothesis was pursued.1

In the 1980s there was further momentum in serotonin research.1 An article by Peroutka and Snyder5 presented the fact that there were multiple 5-HT receptors and classified them as 5-HT1 and 5-HT2, as defined by radioligand binding on brain membranes. Later, 5-HT3 receptors were discovered and 5-HT1 receptors were subdivided into 5-HT1A, 5-HT1B, 5-HT1C, and 5-HT1D. This new understanding of receptor subtypes stimulated the development of various pharmacological agents. The fundamental importance, however, of serotonin is its influence on various biological drives such as appetite, hunger, sex, and sleep, as well as its overall influence on functions of the central nervous system.1

The role of the central serotonin system in psychiatric and behavioral disorders has been recognized as important for a considerable period of time.6 The central serotonin system has projections to the cortex and (most importantly for forensic psychiatry) the limbic system, and as already noted, it is involved in the regulation of a wide range of psychobiological functions. It has also been clearly recognized that the central 5-HT system is involved in impulsive aggression that is directed either toward the self, such as in suicide, or directed outward in various other forms of aggressive behavior.6

The Role of Serotonin in Suicide

The relationship between low concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and cerebrospinal fluid (CSF) in violent suicidal behavior was first reported by Asberg et al. in 1976.9 It was this observation that first led to a hypothesis that low levels of CSF 5-HIAA were associated with suicidal behavior. The relationship of suicide to 5-HT is complex, but appears to have a genetic predisposition.10 The relationship of 5-HT to suicide is based on postmortem studies of 5-HT presynaptic activity (i.e., 5-HT or 5-HIAA) in the brains of suicide victims. (see Mann et al.8 for a review). The finding in most of the studies, was that 5-HT or 5-HIAA was reduced which was consistent with antemortem findings in patients who were suicidal and had low CSF 5-HIAA.7,8 The postmortem findings were consistent across various psychiatric diagnoses.7,8 Subsequently, presynaptic activity was studied by imipramine binding in postmortem brain tissue of suicide victims7,8 It has also been studied by the effects of medication on 5-HT function.7,8 Chronic administration of antidepressants appears to down-regulate the 5-HT receptors. A number of other studies reported similar findings, including those of personality disorder (PD) of individuals who attempted suicide.11,12 Further, there was a reported association between low CSF 5-HIAA and violent suicide attempts13–14 (see Table 1). Suicidal behavior is regarded as aggression directed inward.

The role of 5-HT and aggression was first reported by Yen et al.20 in the animal literature, where it was noted that 5-HT could reduce types of aggression in mice. A large number of animal studies have been completed that mainly show an inverse relationship between isolation-in-
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Table 1
Studies of Central 5-HT Metabolism and Suicide

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject</th>
<th>N</th>
<th>Behavior and Central 5HT Measure&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asberg et al. (1976)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Depressed</td>
<td>68</td>
<td>↓ CSF 5-HIAA in 15 violent suicide attempts</td>
</tr>
<tr>
<td>Brown et al. (1979)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Personality disorder (PD)</td>
<td>22 males</td>
<td>↓ CSF 5-HIAA in suicide attempts</td>
</tr>
<tr>
<td>Traskman et al. (1981)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Suicide attempters (mixed diagnosis)</td>
<td>30</td>
<td>↓ CSF 5-HIAA in suicide attempts</td>
</tr>
<tr>
<td>Brown et al. (1982)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Borderline PD</td>
<td>12</td>
<td>↓ CSF 5-HIAA in suicide attempts</td>
</tr>
<tr>
<td>Van Praag (1982)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Depression</td>
<td>203</td>
<td>↓ CSF 5-HIAA in suicide attempts</td>
</tr>
<tr>
<td>Roy-Byrne et al. (1983)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Bipolar and unipolar depression</td>
<td>45</td>
<td>↓ CSF 5-HIAA did not correlate to suicide attempts</td>
</tr>
<tr>
<td>Banki et al. (1984)&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Depressed female schizophrenics, alcoholics, adjustment disorder</td>
<td>141</td>
<td>↓ CSF 5-HIAA correlates to suicide attempts, particularly to violent attempts across all diagnoses</td>
</tr>
<tr>
<td>Ninan et al. (1984)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Suicidal and nonsuicidal patients</td>
<td>16</td>
<td>↓ CSF 5-HIAA in suicidal patients</td>
</tr>
<tr>
<td>Roy et al. (1986)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Depressed patients</td>
<td>27</td>
<td>↓ low CSF 5-HIAA with suicide attempts (and HVA)</td>
</tr>
</tbody>
</table>

<sup>a</sup>↓ indicates reduced levels.

duced aggression and central 5-HT activity. In other studies, muricidal behavior and various other aspects of aggression have also been related to central 5-HT activity.<sup>6</sup> In broad terms, when central 5-HT activity is low, the tendency is toward impulsive aggression. One hypothesis is that with a lowering of the threshold for aggressive behavior there is an increase in impulsivity.

The presynaptic postmortem studies principally have examined the concentration of 5-HT, 5-HIAA, or imipramine-binding to the postmortem brain tissue (mostly brain stem) from individuals who have committed suicide.<sup>7,8</sup> Significant reductions in 5-HT and/or 5-HIAA concentrations from brain tissue have been reported in many of the published studies.<sup>7,8</sup> This change is independent of psychiatric diagnosis.<sup>8</sup> Imipramine-binding to brain tissue has also been evaluated in suicide perpetrators. This is a presynaptic marker for the serotonergic system.<sup>21,22</sup> The imipramine binding site is seen as a measure of the state of 5-HT neuron terminals. These studies suggest that there may be some structural abnormality in 5-HT function at a presynaptic level in suicidal individuals. The first reports
were by Stanley et al. in 1982 and Stanley and Mann in 1983.

Postsynaptic indices show what appears to be a compensatory response to lowered presynaptic activity, with increased binding of radioligands to the 5-HT2 postsynaptic receptor. Stanley and Mann first reported an increase in the 5-HT2 receptor in the frontal cortex of suicide victims who committed suicide by violent means as compared with matched control subjects. This has now been replicated by these authors and other researchers.

The antemortem human studies looking at presynaptic indices, starting with Asberg et al. and the follow-up studies show concentrations of 5-HT and 5-HIAA at lower than normal levels in most clinical studies of patients who have attempted suicide, which supports the hypothesis that reduced presynaptic 5-HT activity is associated with suicide attempts. Observing that a number of suicidal patients were aggressive, and that violent suicide attempts were associated with reduced central 5-HT functions, Brown et al., Berglund, and Coccaro considered the possible association between low 5-HIAA and violence. According to Coccaro, there are about 13 studies that have looked at this relationship between presynaptic 5-HT activity and aggression. Coccaro reports the majority of the studies measure CSF 5-HIAA. He includes one of the studies completed by Virkkunen et al. in 1987, which relates to arsonists and which confuses the picture. There are, however, a significant number of studies that show a relationship between lowered CSF 5-HIAA and aggression and violent suicide attempts.

These studies need to be looked at in more detail, particularly in terms of how they document a relationship between aggression and low CSF 5-HIAA. Most of these studies followed the Asberg et al. study of 68 depressed patients. Asberg et al. reported that depressed patients who attempted suicide had low CSF 5-HIAA compared with high CSF 5-HIAA in a bimodal distribution. This finding supported the hypothesis that suicide attempts appear to be associated with low presynaptic 5-HT activity. This was followed up by two studies by Brown et al. in 1979 and 1982 that looked at specific personality-disordered individuals. The 1979 Brown et al. study looked at 22 individuals with DSM-II criteria for personality disorder and found that individuals with a history of suicidal acting out had lower CSF 5-HIAA levels. In the 1982 Brown et al. study, 12 individuals with borderline PD (DSM-III) showed a relationship between low CSF 5-HIAA and a history of aggression and suicide attempts. It was also noted that there was an inverse relationship between low CSF 5-HIAA and the MMPI PD scale. A study by Traskman et al. in 1981 supported the finding that CSF 5-HIAA levels were significantly lower in a group of patients they studied who had made a violent suicide attempt (defined as hanging, drowning, shooting, gassing or several deep lacerations) as opposed to individuals who had made a nonviolent suicide attempt (mostly defined as overdoses). Similarly, a study by Banki and Arato in 1983 found that in 141 psychiatric patients suffering from depression and other psychiatric conditions, across the diagnostic spectrum CSF 5-HIAA
levels were lower in the violent suicide attempters. Rydin et al. in 1982\textsuperscript{28} studied depressed and/or suicidal patients compared with controls and measured CSF 5-HIAA. They found that Rorschach ratings for hostility and anxiety correlated positively with low 5-HIAA. Linnoila et al.\textsuperscript{29} examined the CSF 5-HIAA levels amongst 36 males charged with murder and attempted murder. They divided them into an impulsive and a nonimpulsive group. They also noted that 17 out of the 36 subjects, with 14 in the impulsive group and 3 in the nonimpulsive group, had committed at least one previous violent crime. These violent recidivists had lower CSF 5-HIAA levels compared with the nonviolent recidivists. A similar relationship was found when violent offenders who had attempted suicide were compared with ones who had not attempted also had significantly lower CSF 5-HIAA levels. Lidberg et al.\textsuperscript{30} studied 16 male homicide perpetrators and found that 5 subjects who had committed a sexually motivated homicide had lower than normal CSF 5-HIAA levels. In the same study they found that alcoholic homicidal offenders had higher CSF 5-HIAA levels than nonalcoholic violent subjects, which contradicts to some of the studies that have posited a relationship between alcoholism and CSF 5-HIAA levels. Brown et al. in 1985,\textsuperscript{31} reevaluating 12 individuals from the 1979–1982 study, reported an inverse relationship between CSF 5-HIAA and behavioral problems during childhood. Van Praag\textsuperscript{32} evaluated 50 patients with depression, 25 who had low CSF 5-HIAA levels and 25 who had normal CSF 5-HIAA and observed the differences between the two groups. He found that the individuals with low CSF 5-HIAA levels were more aggressive toward others as well as being suicidal. According to Mann et al.\textsuperscript{8} despite the relationship between the degree of violence in the suicide attempt and the various biochemical measures of 5-HT metabolism, it is still uncertain whether there is a firmly established relationship.

**The Role of Serotonin in Aggression**

Coccaro in 1989\textsuperscript{6} studied the role of serotonin in aggression and noted that the evidence for reduced central serotonin metabolism is displayed in a variety of studies. These include animal studies and both postmortem and antemortem human studies. In the human postmortem studies, there is evidence of reduced presynaptic 5-HT function (5-HT, 5-HIAA) and imipramine binding to brain tissues in individuals who have committed suicide. What is uncertain is the degree of aggression present prior to the suicide and how violent the suicide was. The postmortem postsynaptic measures of 5-HT function show on balance an increase in 5-HT levels in suicide victims. This is thought to be a compensatory mechanism to reduced presynaptic 5-HT activity, as shown by 5-HT2 postsynaptic receptor radioligand binding in suicide victims. Coccaro relies heavily on antemortem human studies that show a relationship between aggression and low concentrations of 5-HIAA. These have already been reviewed, but the studies of principal significance are those by Brown et al.
Coccaro also considered a study by Linnoila et al.\textsuperscript{29} Sixteen men who were convicted of criminal homicide, 22 men who attempted suicide, and 39 healthy male control subjects were evaluated with regard to CSF 5-HIAA levels. The homicide offenders were all admitted to a department of forensic psychiatry at the Karolinska Institute in Stockholm, Sweden. Anyone who was involved in treatment with psychotropic drugs was excluded. Originally 25 homicide perpetrators were approached, and 16 consented to participate in the study. Members of the suicidal group were all research subjects recruited between 1970 and 1982. Healthy control subjects were randomly selected from volunteers recruited among hospital staff, blood donors, and various other sources. The study showed that men who had killed their sexual partner (homosexual or heterosexual) had low levels of CSF 5-HIAA compared with controls (levels were in the same range as in individuals who were suicidal). The subjects who attempted suicide also had CSF 5-HIAA levels significantly lower than the controls. These subjects also had been involved in alcohol abuse. The authors concluded that in cases in which there were significantly intense negative emotional states (i.e., jealousy, frustration, or fear) relating to homicidal incidents in which the victim was a sexual partner, the perpetrator had a low CSF 5-HIAA level. These conclusions, together with the Linnoila et al. 1983 study\textsuperscript{29} of impulsive offenders and violent suicide attempts seen in psychiatric patients with low CSF 5-HIAA levels, would seem to suggest a link between central serotonin metabolism and violence acts committed in highly charged emotional states. Coccaro also relies on a study of 20 male arsonists by Virkkunen et al. in 1987,\textsuperscript{27} which supports his argument of impulsively aggressive behavior being related to central 5-HT metabolism.
As arsonists tend to have impulse control disorders specifically in the form of pyromania, and are not violent or aggressive in general terms, this study is relevant to the psychobiology of impulse control disorders. Coccaro et al. had studied 20 male patients with DSM-III criteria for personality disorder, subjecting them to a fenfluramine challenge and measuring the prolactin response. This neuroendocrine challenge is a test of postsynaptic 5-HT receptor functioning and indicates the level of sensitivity of the postsynaptic 5-HT receptor. They found that in studying patients with major affective disorder and/or personality disorders by this method it was only the patients with personality disorder comorbidity who displayed an inverse relationship between the prolactin response and impulsive aggression. The patients who were studied had histories of bipolar disorder, suicide attempts, and alcohol abuse. These findings have been supported by other research (see Table 2).

Other recent studies by Fava (1990), Fava et al. (1993) and Rosenbaum et al. (1993) looked at anger attacks in relation to depression. Fava et al. reported on a series of cases in which patients developed sudden anger or rage attacks that were out of character with their overall personalities;
when these individuals were treated with antidepressants these attacks became less frequent. The antidepressants used were desipramine and clomipramine, and the role of central 5-HT metabolism was questioned. These anger attacks were noteworthy in that they were egodystonic, with high levels of autonomic arousal including sweating, flushing, etc. The physical presentation of the anger attacks was similar to panic attacks, although the subjective sense of the emotion was not anxiety or panic. Akiskal et al. (1979) had reported that anger attacks could occur in relation to cyclothymic disorders. Fava et al. (1993) in a follow-up study looked at anger attacks and unipolar depression. The purpose of the study was to ascertain whether depressed patients with attacks when compared with those without anger attacks were different in some way, and also to establish whether the anger attacks responded to fluoxetine hydrochloride treatment. They found that about 44 percent of outpatients with depression had these anger attacks. These patients were characterized by high levels of anxiety, somatization, and increased hostility compared with patients who did not manifest these attacks. After treatment with fluoxetine hydrochloride, 71 percent of the patients who had anger attacks reported that the attacks had stopped completely. The significant reductions in hostility and anger attacks in depressed patients in response to treatment with fluoxetine hydrochloride suggests that there is some type of central serotonergic dysregulation in this group.

Rosenbaum et al. (1993) did thyroid releasing hormone (TRH) tests in 25 patients diagnosed with major depression, 12 of whom had anger attacks. TRH testing was repeated after eight weeks of treatment with fluoxetine hydrochloride. The results showed that the depressed patients with anger attacks had a blunted prolactin response to TRH stimulation when compared to depressed patients without anger attacks. Treatment with fluoxetine hydrochloride resulted in an increase in prolactin response to TRH, suggesting that the depressed patients with anger attacks may have had some central serotonin dysregulation. The fact that anger attacks respond to fluoxetine hydrochloride, which reverses the results of the TRH stimulation tests, supports the proposed relationship between violence, anger, and serotonin dysregulation. Virkkunen et al. (1994) looked at 43 impulsive and 15 nonimpulsive alcohol offenders and compared them with 21 volunteers in a forensic psychiatry program. CSF was collected from the subjects, and oral glucose and aspartame challenges were then completed. Various other measures were used to quantify their aggressive and impulsive behavior. Alcoholic, impulsive, violent offenders with low CSF 5-HIAA rated high on irritability, impulsivity, and anxiety on psychological rating scales. The study showed that alcoholic and impulsive offenders with antisocial personality disorder had low CSF 5-HIAA, as well as low corticotrophin levels, although they showed a high mean CSF testosterone concentration. CSF 5-HIAA and blood glucose were evaluated after a glucose challenge. Alcoholic and nonimpulsive offenders had significantly higher mean CSF 5-HIAA than all of the other groups. The study showed that low CSF 5-HIAA levels appeared to be correlated with impulsivity, while high CSF testosterone correlated with increased aggressive-
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ness, suspiciousness, social isolation, and other traits.

The serotonergic dysregulation in impulsive violence and aggression is also supported by various clinical pharmacological treatment trials that have been successful in reducing impulsive aggression. Lithium carbonate, used to treat impulsive aggression in double-blind placebo-controlled studies, had been shown to enhance serotonin availability. However, as lithium carbonate also has effects on other neurotransmitters, it is not clear whether its effect on serotonin is what is responsible for the improvement in serotonin availability. Carbamazepine has effects on 5-HT and has also been observed to assist with regulating some impulsive aggression. Because of lack of controlled studies other than case reports using this particular medication, further comments are difficult to make.43

The Role of Serotonin in Impulse Control Disorders

In reviewing studies on suicide and on aggression and violence, an overlap is found between impulsivity and impulse control disorders. The role of serotonin in impulsivity is particularly relevant to the studies (already discussed) by Brown et al., Linnoila et al., and Virkkunen et al.42

McElroy et al. reviewed the DSM-III-R impulse control disorders not elsewhere classified, in terms of family history, criminology, and response to treatment, and suggested that they may be part of an “affective disorder” spectrum. The one feature however, of impulse control disorders not elsewhere classified is that they are clinical entities in which impulsivity is an issue. In addition to the phenomenology of the impulse control disorder, there have been a series of clinical pharmacological interventions in the treatment of impulse control disorders (i.e., intermittent explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania) using a variety of pharmacological agents for treating mood disorders. These include carbamazepine, lithium, desipramine, clomipramine, amitriptyline, trazodone, fluoxetine, and others. (See McElroy et al., 1992 for review.) While these are case reports and open studies, not double-blind studies, they suggest that impulse control disorders respond to thymoleptic agents.51

McElroy et al. (1991) studied 20 consecutive inpatients and outpatients with current or past kleptomania according to DSM-III-R criteria. Their family histories were assessed blindly. All the patients with kleptomania had a lifetime diagnosis of major mood disorders. Eighty percent had a diagnosis of anxiety disorder, and 60 percent had a lifetime diagnosis of eating disorders. A significant proportion of them reported a reduction of their kleptomaniac activity when they were treated with a variety of antidepressants. First-degree relatives of these patients also showed a high morbid risk of mood disorder. Fluoxetine featured strongly among the treatment choices, as did lithium and trazodone, all of which affect 5-HT levels. Virkkunen et al. (1987) studied 20 arsonists, 20 habitually violent offenders, and 10 healthy inpatient volunteers, observing CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) and 5-HIAA levels. The arsonists studied, although they did not necessarily fit the category of pyro-
mania, were regarded as impulsive. MHPG and 5-HIAA levels were lower in the arsonists than in the other two groups. Glucose tolerance tests showed that 30 patients with repeat firesetting behaviors correlated to a hypoglycemic response, indicating an enhanced insulin response. Most of these arsonists would also qualify for a diagnosis of alcohol abuse. In a follow-up study, Virkkunen et al. (1989) studied 58 violent offenders and impulsive firesetters, analyzing them for a history of suicide attempts. The individuals who had a history of suicide attempts, to the extent of requiring admission to a psychiatric facility, had significantly lower CSF 5-HIAA and MHPG levels than individuals who made no such attempts. They concluded that low CSF 5-HIAA and MHPG levels are associated with a lifetime history of suicide attempts in violent offenders and firesetters. In the same population, Linnoila et al. (1989) found that 56 of 58 violent offenders and impulsive firesetters fulfilled the DSM-III criteria for alcohol abuse. The subjects with alcoholic fathers had lower mean CSF 5-HIAA levels and were more impulsive than subjects without alcoholic fathers. These studies, therefore, link impulsivity and violence with central serotonin metabolism. An additional series of articles by Roy and his colleagues, including Virkkunen and Linnoila, consider similar issues.

Pathological gambling is classified in DSM-III, III-R, and -IV as a disorder of impulse control. Roy et al. (1988) studying 20 gamblers and 20 male control subjects, found that there were no significant differences in the groups with regards to CSF 5-HIAA levels. This finding did not support the hypothesis that as an impulse control disorder, pathological gambling would be associated with low CSF 5-HIAA levels. A partial explanation may be that Linnoila et al. in their study in 1983 found that in violent impulsive criminals, the ones who had the lowest CSF 5-HIAA levels were the antisocial personality disorder group, which is an exclusion criterion for pathological gambling. Gamblers showed some abnormalities in CSF MHPG levels.

It is also important to recognize that there may be some confusion in terms of impulsivity as a symptom, which can occur in a variety of psychiatric conditions, as opposed to the impulse control disorders. The impulse control disorders are intermittent explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania. It is important to note that, on DSM-IV impulse control disorder, not otherwise specified (Impulse Control Disorders NOS) may involve other conditions including substance dependence and paraphilia.

The Role of Serotonin in the Paraphilias

The treatment of sexual offenders is a difficult and complex task, partly because the behavior that is the focus of treatment is pleasurable, arousing, and rewarding to the patient, who therefore may not be highly motivated to change. Cognitive and behavioral treatments require the offender to be motivated to change and compliant to treatment for the treatment to be successful. Antiandrogen medications, such as cyproterone acetate and medroxyprogesterone acetate, reduce
paraphiliac behavior through the suppression of sexual drive. However, it has been suggested by Cooper et al. and Hucker et al. that only a small proportion of patients may voluntarily take this type of medication, and because of the potential adverse side effects, these medications are usually reserved for only the most serious sexual offenders. These side effects also limit their use with adolescents. Literature on the treatment of sexual disorders has indicated that serotonin re-uptake inhibitors may be an alternative pharmacological intervention, as they have the efficacy of the androgens and fewer adverse side effects.

There are to date no neurochemical, neuroendocrinological, or neuropharmacological studies of the paraphilias similar to studies of personality disorders, arsonists, and affective disorders. At the present time, as part of an open trial in the treatment of pedophilia with sertraline, my research group is conducting various peripheral measures of central 5-HT. (e.g., [3H]imipramine binding to platelets). These imipramine binding sites on the platelets are closely associated with the presynaptic uptake of 5-HT. These measures will be compared in normal control subjects as well as patients with a diagnosis of depression. One problem is that there is very little known about the comorbidity of the paraphilias and other psychiatric disorders. To try and offset this, studies on comorbidity of the paraphilias are presently underway. It is interesting that in a study on [3H]imipramine binding sites on platelets in obsessive-compulsive disorder (OCD), compared with matched control subjects, the binding sites were found to be 50 percent lower in the OCD group. As there may be a link with OCD and the paraphilias as well as the impulse control disorders, developments in these other areas are important potentially for the treatment and understanding of the nature of the paraphilias.

Because there have been no neurobiological studies of 5-HT in the paraphilias, pharmacological treatment interventions may provide the basis for an understanding of the role of 5-HT in the paraphilias. There is, however, considerable support from the basic sciences for the role of serotonin in sexual behavior. Although the details are beyond the scope of this paper, in general, increased 5-HT activity decreases both male and female sexual activity. In animal research it has been isolated to 5-HT1 sub-receptor systems (i.e., 5-HT1C). There are interesting case reports and a few open trials of specific serotonin re-uptake inhibitors (SSRIs) in the treatment of a variety of paraphilias that suggest the importance of 5-HT in sexual behavior.

The role of serotonin in the treatment of major affective disorders has received considerable attention over the past 20 years. Serotonin re-uptake inhibitors have been used with encouraging results in several placebo-controlled drug trials (Lapierre et al., 1987; Nathan et al., 1990; March et al., 1990). This new group of drugs has also been used with anxiety disorders, including obsessive compulsive disorder, panic disorder, and eating disorder, with success (Westenberg et al., 1987; Perse et al., 1987). Although the paraphilias are not classified as obsessive-compulsive disorders, paraphilics often describe symptoms that are compulsive in nature (Perilstein et al.,...
Apart from the direct effect that serotonin re-uptake inhibition may have on sexual behavior, plasma prolactin levels in rodents, nonhuman primates, and humans increase following serotonergic stimulation, which has a libido-suppressing effect.

The majority of the reports of paraphilics treated with serotonin re-uptake inhibitors are single case reports in which psychotherapy or behavioral therapy was also used. Exhibitionism has been successfully treated with fluoxetine (Bianchi, 1990), and fluvoxamine (Zohar et al., 1994). In this latter case report, the patient was treated under a partial single-blind condition (patient was blind to placebo) with fluvoxamine, desipramine, and a placebo that resembled the fluvoxamine. The impulses to expose and the behavior itself was eliminated with fluvoxamine without affecting sexual desire. Desipramine and the placebo both resulted in the return of the unwanted impulses and behavior.

Fluoxetine has been used successfully to treat both voyeurism (Emmanuel et al., 1991) and cross-dressing (Jorgensen, 1990). Fetishism has also been treated effectively with fluoxetine (Lorefice, 1991).

Kafka and Prentky (1992) successfully treated 10 paraphilics (sexual masochists, sadists, exhibitionists, frotteurs, etc.) and 10 nonparaphilic sexual addicts with fluoxetine in an open trial. From their study, they concluded that fluoxetine reduced the unconventional or deviant sexual desire and behavior while preserving normative sexual arousal.

Perilstein and his associates treated a pedophile, an exhibitionist, and a voyeur/frotteur with fluoxetine. All three patients reported improvements (decrease in deviant fantasies and urges) during the treatment, and this improvement was sustained for three to six months of follow-up.

Stein et al. (1992) reviewed the records of five patients with paraphilias, five with nonparaphilic sexual addictions, and three with sexual thoughts or rituals that met the criteria for obsessive-compulsive disorders, all of whom were treated with fluoxetine, clomipramine, or fluvoxamine. Their results indicated that these medications were most effective in treating the sexual obsessions and compulsions, while the paraphilics responded less to the medications.

A comprehensive review of the various case reports and studies of SSRIs and paraphilias has been presented by Fedoroff. I have felt that there is a considerable overlap between paraphilias and OCDs. This is seen in the natural history of the two conditions as well as in their phenomenology and their mutual response to SSRIs. There is also an overlap between the paraphilias and impulse control disorders.

Conclusions

Research into the neurobiology of the impulse control disorders, the paraphilias, and impulsivity and aggression is of extreme importance to forensic psychiatry. Sadly, with a few exceptions, most forensic psychiatrist in North America are poorly equipped and poorly trained to participate in these developments. Most forensic psychiatrists are not participating in this research or perhaps are not even aware of it.
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European forensic psychiatrists, in contrast, are in the forefront of much of the research. I believe that at least part of the problem in the United States is that there has been so much emphasis on the legal aspects of forensic psychiatry that the average forensic psychiatrist has lost sight of the fundamental clinical basis of forensic psychiatry. The assessment and treatment of the mentally abnormal offender and the study of the mentally abnormal offender through neurobiological and neurobehavioral clinical research is the medical and scientific basis of forensic psychiatry. Enormous opportunities are lost every day and every year as forensic psychiatrists study the law and do not recognize the unique opportunities that confront them in their practices.

The understanding and application of the law is not unique to forensic psychiatry, and there are many people who are better qualified to apply and interpret it. This excessive emphasis on the law continues in our subspeciality examinations and our training. It will, in the long run, undermine forensic psychiatry if we are identified as being expert witnesses with few talents other than being well read in the law, as it applies to a particular legal situation, experience in giving testimony, or an ability to work with attorneys. We are going to lose, and have lost, forensic psychiatrists who could have taught us much but who, as their research interests and strong clinical skills are devalued by comparing them strictly to a knowledge of the law, have drifted off to other academies and organizations. We will meet them in the future in the courtroom, where there clinical research and experience will ensure that their credibility will be recognized as opposed to the “expert witness” forensic psychiatrist.

The serotonin story is really just beginning, and it is critical that we as forensic psychiatrists become involved. It also the time to question some of what we emphasize in our training and our professional organizations, as our ultimate survival may depend on it.

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