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Wien, 29.07.2013
KAD Dr. S/mb

Betrifft: Drogen Warnungen

Sehr geehrte Damen und Herren!

Die Österreichische Ärztekammer übermittelt in der Anlage zu Ihrer Information ein Schreiben der MA 40 Sozial, Sozial- und Gesundheitsrecht, zu o.a. Thematik.

Mit freundlichen Grüßen

KAD Dr. Lukas Stärker e.h.
(i.A. für den Präsidenten)

Anlagen

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‘Green Rolex’ tablets in Scotland, United Kingdom containing PMA, MDMA, PMMA and BZP

Date: 23/07/2013. Issued by: EMCDDA

Information provided by the UK Early warning system.

The ‘Green Rolex’ tablets below have recently been linked to the deaths of a number of people in the Greater Glasgow area, Scotland, United Kingdom. They were found to contain PMA, MDMA, PMMA and BZP.


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REVIEW ARTICLE

CURRENT CONCEPTS

The Serotonin Syndrome

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THE SEROTONIN SYNDROME IS A POTENTIALLY LIFE-THREATENING adverse drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs. Three features of the serotonin syndrome are critical to an understanding of the disorder. First, the serotonin syndrome is not an idiopathic drug reaction; it is a predictable consequence of excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors.[1,2] Second, excess serotonin produces a spectrum of clinical findings.[3] Third, clinical manifestations of the serotonin syndrome range from barely perceptible to lethal. The death of an 18-year-old patient named Libby Zion in New York City more than 20 years ago, which resulted from coadminstration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition.[4]

DEFINITION AND EPIDEMIOLOGY

The serotonin syndrome is often described as a clinical triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities, but not all of these findings are consistently present in all patients with the disorder (Fig. 1).[5,6] Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration.

The incidence of the serotonin syndrome is thought to mirror the increasing number of proserotonergic agents being used in clinical practice.[7] In 2002, the Toxic Exposure Surveillance System, which receives case descriptions from office-based practices, inpatient settings, and emergency departments, reported 26,733 incidences of exposure to selective serotonin-reuptake inhibitors (SSRIs) that caused significant toxic effects in 7349 persons and resulted in 93 deaths.[8,9] The assessment of the serotonin syndrome in therapeutic drug dosing has relied on post-marketing surveillance studies, one of which identified an incidence of 0.4 case per 1000 patient-months for patients who were taking nefazodone.[10] Performing a rigorous epidemiologic assessment of the serotonin syndrome, however, is difficult, since more than 85 percent of physicians are unaware of the serotonin syndrome as a clinical diagnosis.[10] The syndrome occurs in approximately 14 to 16 percent of persons who overdose on SSRIs.[8]

Although the serotonin syndrome has occurred in a broad range of clinical environments, several barriers limit the ability of clinicians to diagnose the condition. First, the syndrome may be missed because of its protean manifestations. Clinicians and patients may dismiss symptoms such as tremor with diarrhea or hypertension as inconsequential or unrelated to drug therapy; anxiety and akathisia may be misattributed to the patient's mental state.[5,10] Second, a strict application of the diagnostic criteria proposed

by Sternbach potentially rules out what are now recognized as mild, early, or subacute cases of the disorder.[1,11] Third, clinicians cannot diagnose a condition of which they are unaware, even though the serotonin syndrome is not rare and has been identified in patients of all ages, including the elderly, children, and newborn infants.[10,12-14]

A striking number of drugs and drug combinations have been associated with the serotonin syndrome (Table 1). These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, SSRIs, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products; the withdrawal of medications has also been associated with the syndrome.[1,4,12,15-23] A single therapeutic dose of an SSRI has caused the serotonin syndrome.[12] Moreover, the addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the condition.[16,24,25] Administration of serotonergic agents within five weeks after the discontinuation of fluoxetine therapy has produced a drug interaction culminating in the serotonin syndrome, presumably the result of the demethylation of fluoxetine to norfluoxetine, a serotonergic metabolite with a longer serum half-life than its parent compound.[13] Specific drugs, such as MAOIs that are irreversible or nonselective or that inhibit monoamine oxidase subtype A, are strongly associated with severe cases of the syndrome, especially when these agents are used in combination with meperidine, dextromethorphan, SSRIs, or methylenedioxymethamphetamine (MDMA, or "ecstasy").[4,8,15,26,27]

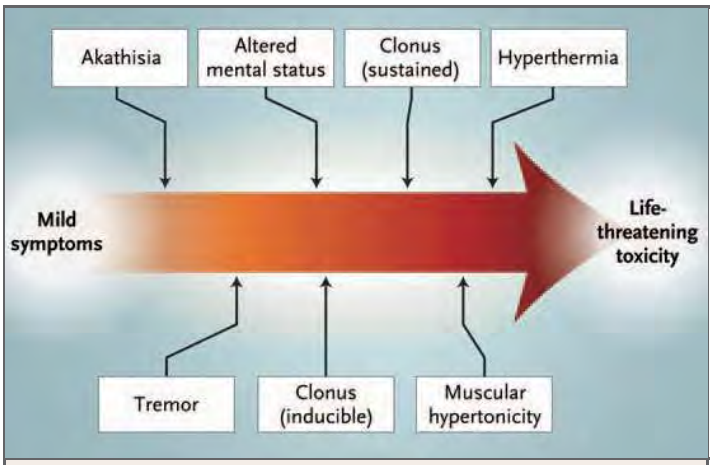

Figure 1. Spectrum of Clinical Findings.
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

MANIFESTATIONS

The serotonin syndrome encompasses a range of clinical findings. Patients with mild cases may be afebrile but have tachycardia, with a physical examination that is notable for autonomic findings such as shivering, diaphoresis, or mydriasis (Fig. 2). The neurologic examination may reveal intermittent tremor or myoclonus, as well as hyperreflexia.

A representative example of a moderate case of the serotonin syndrome involves such vital-sign abnormalities as tachycardia, hypertension, and hyperthermia. A core temperature as high as 40°C is common in moderate intoxication. Common features of the physical examination are mydriasis, hyperactive bowel sounds, diaphoresis, and normal skin color. Interestingly, the hyperreflexia and clonus seen in moderate cases may be considerably greater in the lower extremities than in the upper extremities; patellar deep-tendon reflexes often demonstrate clonus for several seconds after a single tap of the tendon, whereas the brachioradialis reflex is only slightly increased. Patients may exhibit horizontal ocular clonus. Changes in mental status include mild agitation or hypervigilance, as well as slightly pressured speech. Patients may easily startle or adopt a peculiar head-turning behavior characterized by repetitive rotation of the head with the neck held in moderate extension.

In contrast, a patient with a severe case of the serotonin syndrome may have severe hypertension and tachycardia that may abruptly deteriorate into frank shock. Such patients may have agitated delirium as well as muscular rigidity and hypertonicity. Again, the increase in muscle tone is considerably greater in the lower extremities. The muscle hyperactivity may produce a core temperature of more than 41.1°C in life-threatening cases. Laboratory abnormalities that occur in severe cases include metabolic acidosis, rhabdomyolysis, elevated levels of serum aminotransferase and creatinine, seizures, renal failure, and disseminated intravascular coagulopathy. Many of these abnormalities arise, however, as a consequence of poorly treated hyperthermia.

Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.

Drugs associated with the serotonin syndrome

Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolide (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)
Other: lithium

Drug interactions associated with severe serotonin syndrome

Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron
Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolide and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

To better delineate the signs and symptoms that define the serotonin syndrome, the clinical findings in 2222 consecutive cases of self-poisoning with serotonergic drugs were rigorously assessed on the basis of information from a detailed toxicology registry.[2] These findings were then compared with the "gold standard," the assignment of a diagnosis of the serotonin syndrome by a medical toxicologist.[2] The clinical findings that had a statistically significant association with the diagnosis of the syndrome were primarily neuromuscular, including hyperreflexia, inducible clonus, myoclonus, ocular clonus, spontaneous clonus, peripheral hypertonicity, and shivering.[2] Autonomic derangements were tachycardia on admission, mydriasis, diaphoresis, and the presence of bowel sounds and diarrhea.[2] Abnormalities in mental status that were significantly associated with the serotonin syndrome were agitation and delirium.[2] Hyperthermia that was caused by muscular hypertonicity, defined in this study as a temperature of more than 38°C, was not as strongly associated with the diagnosis of the serotonin syndrome but occurred in severely intoxicated patients.[2]

The onset of symptoms is usually rapid, with clinical findings often occurring within minutes after a change in medication or self-poisoning.[28] Approximately 60 percent of patients with the serotonin syndrome present within six hours after initial use of medication, an overdose, or a change in dosing.[28] Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death. The serotonin syndrome is not believed to resolve spontaneously as long as precipitating agents continue to be administered.

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Serotonin is produced by the decarboxylation and hydroxylation of L-tryptophan. Its quantity and actions are tightly regulated by a combination of reuptake mechanisms, feedback loops, and metabolizing enzymes (Fig. 3). Serotonin receptors are divided into seven 5-hydroxytryptamine (5-HT) families (5-HT_1 to 5-HT_7), several of which have multiple members (e.g., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}). Further structural and operational diversity is achieved by allelic polymorphisms, splice variants, receptor isoforms, and the formation of receptor heterodimers.[29]

Serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, located in the brain stem from the midbrain to the medulla.[30] The rostral end of this system assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior.[30] The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone.[30] In the periphery, the serotonin system assists in the regulation of vascular tone and gastrointestinal motility.[30]

No single receptor appears to be responsible for the development of the serotonin syndrome, although several lines of evidence converge to suggest that agonism of 5-HT_{2A} receptors contributes substantially to the condition.[31-35] Additional subtypes of serotonin receptors, such as 5-HT_{1A}, may contribute through a pharmacodynamic interaction in which increased synaptic concentrations of serotonin agonist saturate all receptor subtypes. Nora-

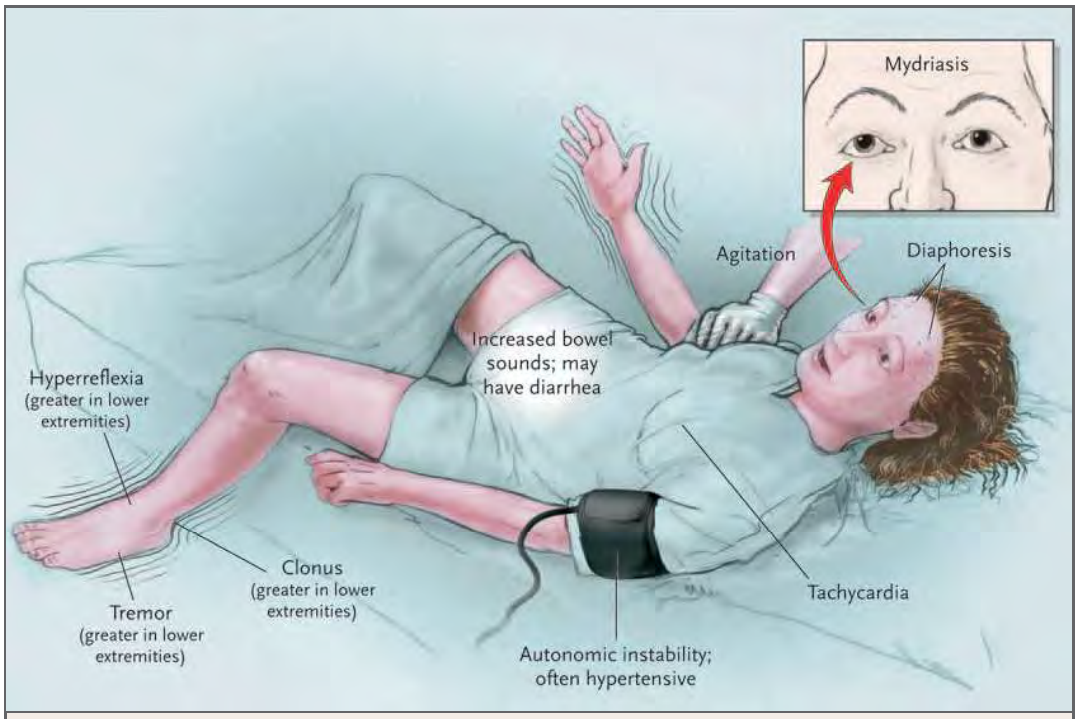

Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

drenergic CNS hyperactivity may play a critical role, since the degree to which CNS norepinephrine concentrations are increased in the serotonin syndrome may correlate with the clinical outcome.[33,35,36] Other neurotransmitters, including *N*-methyl-D-aspartate (NMDA) receptor antagonists and γ-aminobutyric acid (GABA), may affect the development of the syndrome, but the role of these agents is less clear.[33,37] Dopaminergic receptors have been implicated, but this association may arise from pharmacodynamic interactions, direct interactions between serotonin and dopamine receptors, other mechanisms, or a misdiagnosis of the serotonin syndrome as the neuroleptic malignant syndrome.[26,33,38,39]

DIAGNOSIS

No laboratory tests confirm the diagnosis of the serotonin syndrome. Instead, the presence of tremor, clonus, or akathisia without additional extrapyramidal signs should lead clinicians to consider the diagnosis, which must be inferred from the patient's history and physical examination. When obtaining the patient's history, clinicians should inquire about the use of prescription and over-the-counter drugs, illicit substances, and dietary supplements, since all of these agents have been implicated in the development of the serotonin syndrome. The evolution of symptoms and their rate of change should also be reviewed. Physical examination should include a focused assessment of deep-tendon reflexes, clonus, and muscle rigidity, in addition to an evaluation of the size and reactivity of the pupils, the dryness of the oral mucosa, the intensity of bowel sounds, skin color, and the presence or absence of diaphoresis.

Although several diagnostic criteria have been developed, we prefer the decision rules described in Figure 4.[2,11,14,40] These rules, when compared with the original diagnostic criteria, are simpler, more sensitive (84 percent vs. 75 percent), and more specific (97 percent vs. 96 percent) for diagnosing the serotonin syndrome.[1,2] Clonus (inducible, spontaneous, and ocular) is the most important finding in establishing the diagnosis of the serotonin syndrome.[2,27,41] Clinicians should always be aware

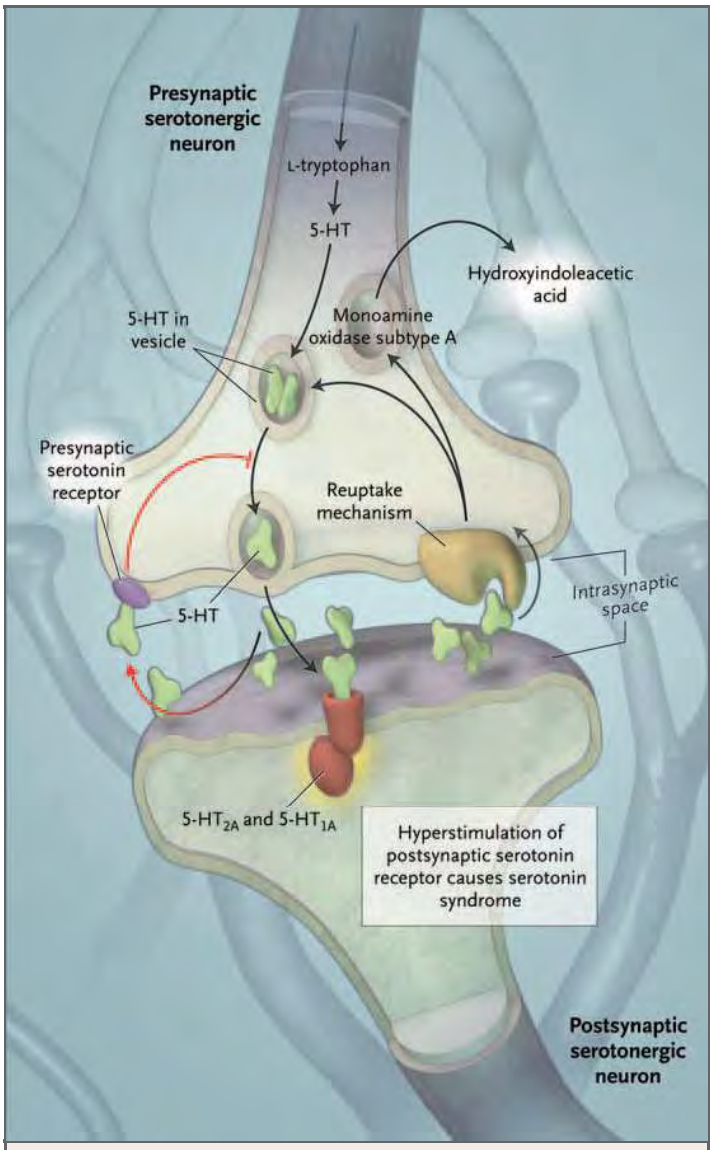

Figure 3. Serotonin Biosynthesis and Metabolism.

Serotonin is produced in presynaptic neurons by hydroxylation and decarboxylation of L-tryptophan. Serotonin is then incorporated into vesicles, where it resides until it is needed for neurotransmission. After axonal stimulation, serotonin is released into the intrasynaptic space; presynaptic serotonin receptors function as a feedback loop to inhibit exocytosis of vesicles (shown in red). Serotonin then binds to postsynaptic receptors to effect neurotransmission. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron, where it is reintroduced into vesicles. Serotonin is then metabolized by monoamine oxidase subtype A to hydroxyindoleacetic acid.

that hyperthermia and hypertonicity occur in life-threatening cases, but muscle rigidity may mask the highly distinguishing findings of clonus and hyperreflexia and therefore cloud the diagnosis.[2,42]

The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and the neuroleptic malignant syndrome, each of which can be readily distinguished from the serotonin syndrome on clinical grounds and on the basis of the medication history (Table 2). Patients with the anticholinergic syndrome have normal reflexes and show the "toxidrome" of mydriasis; agitated delirium; dry oral mucosa; hot, dry, erythematous skin; urinary retention; and an absence of bowel sounds. Hyperactive bowel sounds — along with neuromuscular abnormalities, diaphoresis, and normal skin color — distinguish the serotonin syndrome from the anticholinergic toxidrome.[2]

Malignant hyperthermia is a pharmacogenetic disorder characterized by increasing concentrations of end-tidal carbon dioxide, hypertonicity, hyperthermia, and metabolic acidosis. The disorder occurs within minutes after exposure to inhalational anesthetic agents.[43] On physical examination, the skin is often mottled, with cyanotic areas contrasting with patches of bright red flushing.[43] The rigor mortis–like rigidity of skeletal muscles and hyporeflexia that are seen in malignant hyperthermia further distinguish this condition from the serotonin syndrome.[43]

The neuroleptic malignant syndrome is an idiopathic reaction to dopamine antagonists, a condition that is defined by a slow onset, bradykinesia or akinesia, "lead pipe" muscular rigidity, hyperthermia, fluctuating consciousness, and autonomic instability.[44] Signs and symptoms of the neuroleptic malignant syndrome typically evolve during several days, in contrast to the rapid onset and hyperkinesia of the serotonin syndrome. Knowledge of the precipitating drug also helps in distinguishing between syndromes: dopamine antagonists produce bradykinesia, whereas serotonin agonists produce hyperkinesia.[45]

MANAGEMENT

Management of the serotonin syndrome involves the removal of the precipitating drugs, the provision of supportive care, the control of agitation, the administration of 5-HT_{2A} antagonists, the control of autonomic instability, and the control of hyperthermia.[45] Many cases of the serotonin syndrome typically resolve within 24 hours after the initiation of therapy and the discontinuation of serotonergic drugs, but symptoms may persist in patients taking drugs with long elimination half-lives, active metab-

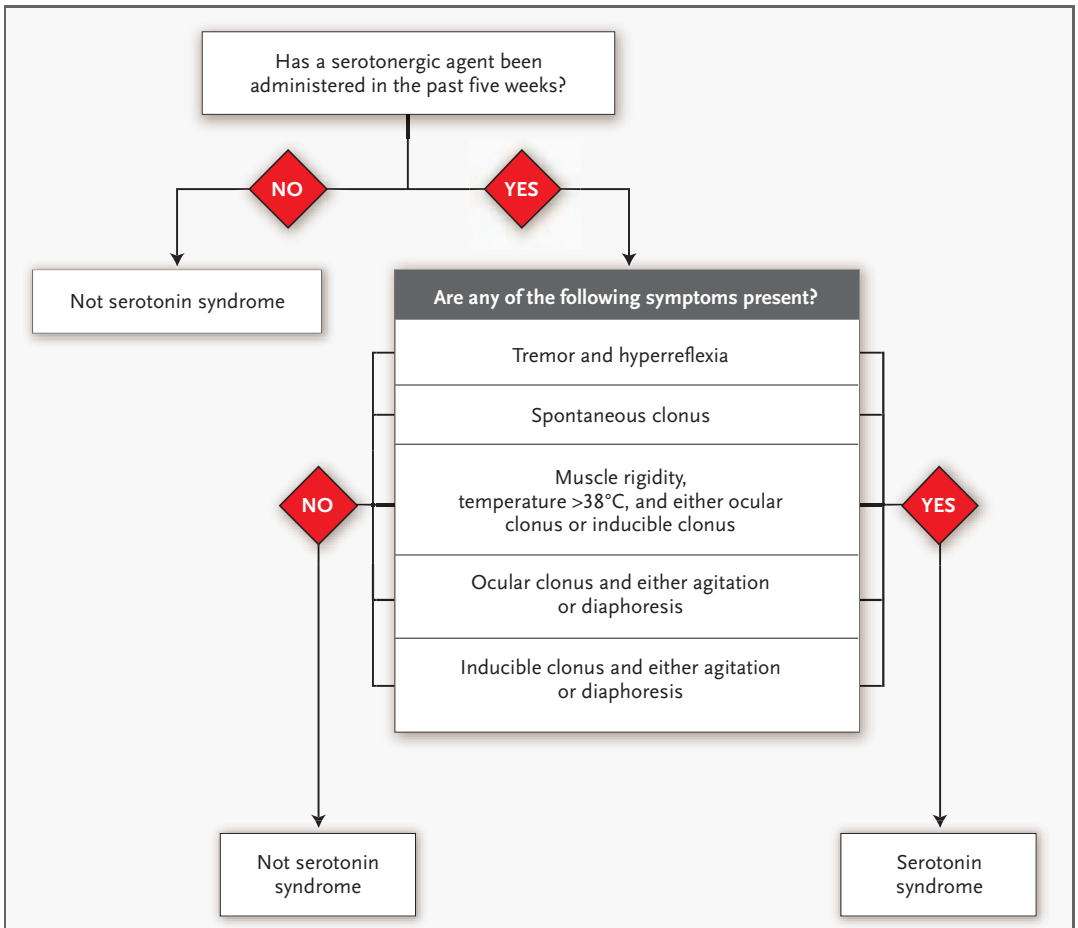

Figure 4. Algorithm for Diagnosis.

The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular findings and mask the diagnosis. Criteria adapted from Dunkley.[2]

olites, or a protracted duration of action. Supportive care, comprising the administration of intravenous fluids and correction of vital signs, remains a mainstay of therapy. However, an abrupt deterioration in the condition of a patient who has been conservatively treated indicates the need for an immediate, aggressive response.[1,2,45]

The intensity of therapy depends on the severity of illness. Mild cases (e.g., with hyperreflexia and tremor but no fever) can usually be managed with supportive care, removal of the precipitating drugs, and treatment with benzodiazepines. Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected and may benefit from the administration of 5-HT_{2A} antagonists. Hyperthermic patients (those whose temperature is more than 41.1°C) are severely ill and should receive the above therapies as well as immediate sedation, neuromuscular paralysis, and orotracheal intubation.

Control of agitation with benzodiazepines is essential in the management of the serotonin syndrome, regardless of its severity. Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome.[37,45] Physical restraints are ill-advised and may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.[46] If physical restraints are used, they must be rapidly replaced with chemical sedation.

Pharmacologically directed therapy involves the

Table 2. Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions.

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Pupils	Mucosa	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental Status
Serotonin syndrome	Proserotonergic drug	<12 hr	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Mydriasis	Sialorrhea	Diaphoresis	Hyperactive	Increased, predominantly in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mydriasis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonist	1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Normal	Sialorrhea	Pallor, diaphoresis	Normal or decreased	"Lead-pipe" rigidity present in all muscle groups	Bradyreflexia	Stupor, alert mutism, coma
Malignant hyperthermia	Inhalational anesthesia	30 min to 24 hr after administration of inhalational anesthesia or succinylcholine	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled appearance, diaphoresis	Decreased	Rigor mortis–like rigidity	Hyporeflexia	Agitation

administration of 5-HT_{2A} antagonists.[7,45] Cyproheptadine is the recommended therapy for the serotonin syndrome, although its efficacy has not been rigorously established.[7,45] Treatment of the serotonin syndrome in adults may require 12 to 32 mg of the drug during a 24-hour period, a dose that binds 85 to 95 percent of serotonin receptors.[47] Clinicians should consider an initial dose of 12 mg of cyproheptadine and then 2 mg every two hours if symptoms continue. Maintenance dosing involves the administration of 8 mg of cyproheptadine every six hours. Cyproheptadine is available only in oral form, but tablets may be crushed and administered by nasogastric tube. Atypical antipsychotic agents with 5-HT_{2A}–antagonist activity may be beneficial in treating the serotonin syndrome. The sublingual administration of 10 mg of olanzapine has been used successfully, but its efficacy has not been rigorously determined.[48] Clinicians desiring a parenteral agent should consider the intramuscular administration of 50 to 100 mg of chlorpromazine.[45] Even though chlorpromazine is an outdated therapy that has been replaced in psychiatric practice by newer agents, its use may nonetheless be considered in severe cases.[45]

Control of autonomic instability involves stabilization of fluctuating pulse and blood pressure. Hypotension arising from MAOI interactions should be treated with low doses of direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, and epinephrine). Direct agonists do not require intracellular metabolism to generate a vasoactive amine, but their concentration in the synapse is regulated by catecholamine-O-methyl transferase. Indirect agents such as dopamine are metabolized to epinephrine and norepinephrine. Under normal conditions, monoamine oxidase limits the intracellular concentration of these metabolites. When inhibited, however, monoamine oxidase cannot control the amount of epinephrine and norepinephrine produced, and an exaggerated hemodynamic response may ensue. Patients in whom hypertension and tachycardia develop, either as a result of pressor therapy or from poisoning itself, should be treated with short-acting agents such as nitroprusside and esmolol.

Control of hyperthermia involves eliminating excessive muscle activity. Although benzodiazepines have a beneficial effect in moderate cases, in severely ill patients with hyperthermia (a temperature of more than 41.1°C) immediate paralysis should be induced with nondepolarizing agents such as ve-

curonium, followed by orotracheal intubation and ventilation. Clinicians should avoid succinylcholine because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. Recent case reports have shown that premature termination of neuromuscular paralysis was associated with a recrudescence of hyperthermia.[49] There is no role for antipyretic agents in the management of the serotonin syndrome; the increase in body temperature is due to muscular activity, not an alteration in the hypothalamic temperature set point.

Potential pitfalls for clinicians include misdiagnosis of the serotonin syndrome, a failure to comprehend its rapidity of progression, and adverse effects of pharmacologically directed therapy. The diagnosis may be clouded by the presence of severe muscle rigidity that obscures myoclonus and hyperreflexia. If the correct diagnosis is not obvious, a prudent course is to withhold antagonist therapy and provide aggressive supportive care, sedation with benzodiazepines, and, if necessary, intubation and paralysis.[7] Because of the speed with which the condition of patients declines, physicians should anticipate the need for aggressive therapy before clinical indications are reached.

Therapies such as propranolol, bromocriptine, and dantrolene are not recommended.[7,45] Propranolol, a 5-HT_{1A} antagonist with a long duration of action, may cause hypotension and shock in patients with autonomic instability. Furthermore, propranolol can abolish tachycardia that can be used to determine the duration and effectiveness of therapy.[2] Bromocriptine, a dopamine agonist, and dantrolene are not useful therapies; case reports citing their use probably involved a misdiagnosis of another condition as the serotonin syndrome.[7,35,45] Bromocriptine has been implicated in the development of the serotonin syndrome, and its use in patients in whom the neuroleptic malignant syndrome is misdiagnosed may worsen serotonergic signs.[27,50] According to one report, the administration of bromocriptine and dantrolene to a patient with the serotonin syndrome caused an abrupt increase in temperature, culminating in death.[39] This finding is supported by the observation that dantrolene has no effect on survival in animal models.[34,35]

Antagonist therapy with the use of cyproheptadine and chlorpromazine may have unintended effects. The dosage of cyproheptadine used to treat the serotonin syndrome may cause sedation, but this effect is a goal of therapy and should not deter clinicians from using the drug. Chlorpromazine is an outmoded drug that has been associated with severe orthostatic hypotension and has been thought to aggravate hyperthermia. Patients who require acute parenteral therapy for the serotonin syndrome are often hypertensive and are not ambulatory, so that the risk of orthostatic hypotension is minimized. Hyperthermia in response to neuroleptic administration is an idiopathic response; the normal outcome is hypothermia. Nonetheless, chlorpromazine should not be administered to a patient with hypotension or the neuroleptic malignant syndrome, since the drug could potentially exacerbate clinical findings.

PREVENTION

The serotonin syndrome can be avoided by a combination of pharmacogenomic research, the education of physicians, modifications in prescribing practices, and the use of technological advances. The application of pharmacogenomic principles can potentially protect patients at risk for the syndrome before the administration of serotonergic agents. Once toxicity occurs, consultation with a medical toxicologist, a clinical pharmacology service, or a poison-control center can identify proserotonergic agents and drug interactions, assist clinicians in anticipating adverse effects, and provide valuable clinical decision-making experience. The avoidance of multidrug regimens is critical to the prevention of the serotonin syndrome. If multiple agents are required, however, computer-based ordering systems and the use of personal digital assistants can detect drug interactions and decrease reliance on memory in drug ordering. Post-marketing surveillance linked to physician education has been proposed to improve awareness of the serotonin syndrome.[10]

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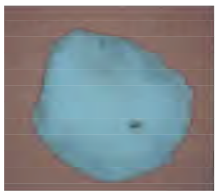
AKTUELLE WARNUNGEN UND BESONDERE ERGEBNISSE Juli 2013

Seit Anfang Juli hat **checkit!** eine Reihe an gesundheitlich bedenklichen Substanzen getestet. Unter anderem wurde in vier vermeintlichen Speed-Proben erneut die neue psychoaktive Substanz **4-Methylamphetamin (4-MA)** identifiziert. Neben Amphetamin und Koffein enthielt jede Probe 4-MA in unterschiedlichen Dosierungen (bis zu 228 Milligramm pro Gramm). Da es im Zusammenhang mit dem Konsum von 4-MA europaweit bereits zu mehreren Todesfällen gekommen ist, raten wir dringend vom Konsum ab!

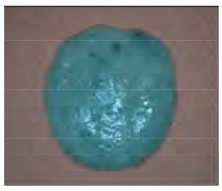
Außerdem wurde in einer als MDMA in Pulverform zur Analyse gebrachten Substanz das Ketamin-Derivat **Methoxetamin** gefunden. Auch in Zusammenhang mit dem Konsum von Methoxetamin wurden bereits Todesfälle gemeldet. Auf Grund dieser Tatsachen und da eine unerwartete dissoziative Wirkung unter Umständen sehr unangenehm sein kann, raten wir dringend zur Vorsicht.

Im Folgenden werden alle Proben, die im Zeitraum von 1.Juli 2013 bis dato bei **checkit!** analysiert und als hoch dosiert, unerwartet oder gesundheitlich besonders bedenklich eingestuft wurden, detailliert dargestellt.

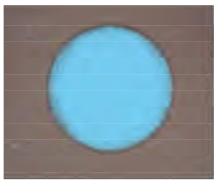
Als „Ecstasy" zur Analyse gebracht:



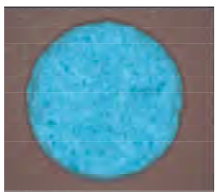
Logo: nicht erkennbar
Rückseite: -
Farbe: weiß
Durchmesser: Bruchstück
Dicke: Bruchstück
Inhaltsstoffe: **BZP + MeOPP + Koffein + TFMPP**



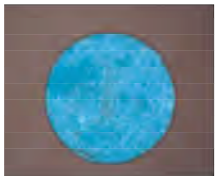
Logo: -
Rückseite: -
Farbe: blau
Durchmesser: 1,17 mm
Dicke: 0,3 mm
Inhaltsstoffe: **MDMA (5 mg) + BZP + MeOPP + Koffein (3 mg) + TFMPP (2 mg) + unbekannte Substanz**



Logo: Rose
Rückseite: Bruchrille
Farbe: weiß
Durchmesser: 8,2 mm
Dicke: 4 mm
Inhaltsstoffe: **TFMPP + pFPP**



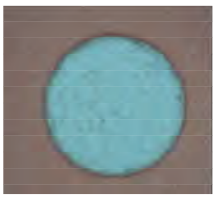
Logo: -
Rückseite: -
Farbe: hell blau
Durchmesser: 11,1 mm
Dicke: 3,7 mm
Inhaltsstoffe: **Koffein (69 mg) + 4-MEC (1 mg)**



Logo: 1
Rückseite: Bruchrille
Farbe: hell blau
Durchmesser: - mm
Dicke: - mm
Inhaltsstoffe: **Koffein (135 mg)**

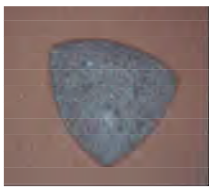
Hoch Dosiert:

Logo: Redbull
Rückseite: -
Farbe: rosa
Durchmesser: - mm
Dicke: - mm
Inhaltsstoffe: **MDMA (103 mg)**



Logo: „Apple"-Logo
Rückseite: -
Farbe: gelb
Durchmesser: 8,2 mm
Dicke: 4,8 mm
Inhaltsstoffe: **MDMA (113 mg)**

Logo: -
Rückseite: -
Farbe: rosa
Durchmesser: 9,4 mm
Dicke: 4,9 mm
Inhaltsstoffe: **MDMA (133 mg)**



Logo: -
Rückseite: -
Farbe: lila
Durchmesser: 14 mm
Dicke: 4,5 mm
Inhaltsstoffe: **MDMA (175 mg)**

Logo: Redbull
Rückseite: -
Farbe: orange
Durchmesser: - mm
Dicke: - mm
Inhaltsstoffe: **MDMA (204 mg)**

Als MDMA (Kristall, Pulver, Kapsel) zur Analyse gebracht:

Tatsächliche Inhaltsstoffe:

- MDMA (67 mg/g) + 4 –MEC (427 mg/g)
- Methylon (671 mg/g)
- Methylon (771 mg/g)

- Methylon (566 mg/g)
- 4-MEC (930 mg/g)
- Methylon (924 mg/g)
- Methoxetamin (153 mg/g)

Als „Speed" zur Analyse gebracht:

Tatsächliche Inhaltsstoffe:

- Amphetamin (71 mg/g) + Paracetamol (201 mg/g) + Koffein (438 mg/g)
- Amphetamin (529 mg/g) + Koffein (223 mg/g) + zwei unbekannte Substanzen
- Amphetamin (169 mg/g) + Paracetamol (33 mg/g) + Koffein (273 mg/g) + Acetylsalicylsäure
- Amphetamin (103 mg/g) + Koffein (470 mg/g) + unbekannte Substanz
- Amphetamin (204 mg/g) + Koffein (392 mg/g) + **4-Methylamphetamin** (76 mg/g)
- Amphetamin (250 mg/g) + Koffein (498 mg/g) + **4-Methylamphetamin** (190 mg/g)
- Amphetamin (242 mg/g) + Koffein (469 mg/g) + **4-Methylamphetamin** (228 mg/g)
- Amphetamin (266 mg/g) + Koffein (497 mg/g) + **4-Methylamphetamin** (162 mg/g)
- 4-MEC (1 mg/g)

Als Kokain zur Analyse gebracht:

Tatsächliche Inhaltsstoffe:

- Kokain (461 mg/g) + Phenacetin (259 mg/g)
- Kokain (582 mg/g) + Levamisol (25 mg/g)
- Kokain (602 mg/g) + Levamisol (320 mg/g)
- Kokain (234 mg/g) + Levamisol (21 mg/g)
- Kokain (167 mg/g) + Levamisol (34 mg/g) + Phenacetin (143 mg/g)
- Kokain (103 mg/g) + Levamisol (14 mg/g) + Phenacetin (222 mg/g) + Lidocain (70 mg/g)
- Kokain (220 mg/g) + Levamisol (51 mg/g) + Paracetamol (1 mg/g)

Als LSD zur Analyse gebracht:

Tatsächliche Inhaltsstoffe: **drei unbekannte Substanzen**

Zur Analyse gebracht als:

- Ketamin → tatsächliche(r) Inhaltsstoff(e): Ketamin (861 mg/g) + MDMA (23 mg/g)
- Ketamin → tatsächliche(r) Inhaltsstoff(e): Amphetamin (33 mg/g) + Koffein (121 mg/g) + unbekannte Substanz
- Kokain + Amphetamin → tatsächliche(r) Inhaltsstoff(e): MDPV (221 mg/g) + unbekannte Substanz
- 2C-B → tatsächliche(r) Inhaltsstoff(e): 2C-B + Koffein+ unbekannte Substanz
- 2C-B → tatsächliche(r) Inhaltsstoff(e): 2C-B+ MDMA (26 mg) + unbekannte Substanz

Weiterführende Infos zu Inhaltsstoffen: *(in alphabethischer Reihenfolge)*

BZP (1-Benzylpiperazin) gehört zur Gruppe der Piperazine und ähnelt hinsichtlich der Wirkung Amphetaminen bzw. Amphetaminderivaten, wie MDMA. Durch die Kombination von BZP und MDMA kann es zu einer bedrohlichen Erhöhung von Herzschlag und Blutdruck kommen. Auch das Mischen mit anderen Substanzen - insbesondere mit Alkohol - kann sehr gefährlich sein. Die Wechselwirkungen sind kaum einschätzbar und die Belastung für Körper und Psyche besonders groß.

Levamisol ist ein Anthelminthikum (wird in der Tiermedizin gegen Wurmbefall eingesetzt), welches früher auch in der Humanmedizin Anwendung fand. Als Beimengung zu Kokain tritt die Substanz in den letzten Jahren gehäuft auf. Verschiedene Nebenwirkungen, die im Zusammenhang mit Levamisol berichtet wurden, sind unter anderem: allergische Reaktionen (Schwierigkeiten beim Atmen, Anschwellen der Lippen, der Zunge, des Gesichts) und Beeinträchtigung des zentralen Nervensystems (z.B. Verwirrungszustände oder Bewusstlosigkeit, extreme Müdigkeit)[1]. Die bedenklichste Nebenwirkung von Levamisol ist die Veränderung des Blutbildes, Agranulocytosis genannt. Im Zuge dieser kommt es zu einer Reduktion der weißen Blutkörperchen, was in weiterer Folge – auf Grund von Immunschwäche – zu lebensbedrohlichen Infektionen führen kann.

Lidocain ist ein Lokalanästhetikum, das sowohl in der Veterinär- als auch in der Humanmedizin als gut und schnell wirksames örtliches Betäubungsmittel eingesetzt wird.

MDPV (Methylenedioxypyrovaleron) gehört zur Gruppe der Stimulanzien und ist - wie andere Research Chemicals - bis dato sehr wenig erforscht. Die Wirkung ist in erster Linie stimulierend. Zu den positiven Effekten zählen unter anderem Euphorie, erhöhte Empathie und Geselligkeit, gesteigertes Redebedürfnis und geistige Klarheit. Es werden auch aphrodisierende Effekte beschrieben. Negative Wirkungen sind Appetitverlust, Schlafschwierigkeiten, unwillkürliche Körperbewegungen (z.B. Zuckungen), Verwirrung, Nervosität und Ängstlichkeit. Das „Runterkommen" wird häufig als sehr unangenehm beschrieben, was gelegentlich zu erneutem „Nachlegen" führt. Risiken und Langzeitfolgen sind unbekannt.

4-MEC (Methylethylcathinon) gehört zu der Gruppe der Cathinone und ist von der Wirkungsweise her dem 4-Methylmethcathinon (Mephedron) sehr ähnlich, möglicherweise aber potenter. Die Wirkung ist in erster Linie stimulierend und euphorisierend. UserInnen-Berichten zur Folge kommt es schnell zu einer Toleranzentwicklung. Ein erhöhtes psychisches Abhängigkeitspotential ist - durch die strukturelle Ähnlichkeit zu Mephedron - mit hoher Wahrscheinlichkeit gegeben.

Methylamphetamin (4-MA) ist mit Amphetamin eng verwandt und wurde in der Vergangenheit auf die mögliche Eigenschaft als Appetitzügler untersucht, allerdings wurde die Forschung dazu nie abgeschlossen. In jüngerer Zeit ist die Substanz in diversen europäischen Ländern als „Designer Droge" aufgetaucht. In Zusammenhang mit 4-MA ist es bereits zu mehreren Vergiftungen bzw. ungeklärten Todesfällen in den Niederlanden, Belgien und Großbritannien gekommen. Aus Belgien wurden Ende April 2012 zwei weitere Todesfälle gemeldet. 4-MA bewirkt – ähnlich wie MDMA - eine Ausschüttung der

[1] Kinzie E. Levamisole found in patients using cocaine. Annals of Emergency Medicine 2009 (53) 546-547.

Neurotransmitter Dopamin, Noradrenalin und Serotonin. In Tierversuchen hat sich gezeigt, dass eine zu MDMA vergleichsweise erhöhte Ausschüttung dieser Botenstoffe erfolgt. Die Wirkung scheint der von MDMA ähnlich zu sein – euphorische Effekte sind wahrscheinlich. Die Antriebssteigerung ist aber vergleichsweise stark und eher mit Amphetamin vergleichbar. 4-MA wirkt vermutlich schon in sehr geringen Dosen, ein Nachlegen soll sehr negative Effekte - bis hin zum Serotoninsyndrom[2]- bewirken. Da es sich bei 4-MA um eineunerforschte Substanz handelt, die im Verdacht steht stark neurotoxisch zu sein, raten wir dringend vom Konsum von 4-MA ab.

MeOPP (*para*-Methoxyphenylpiperazin) ist ein Piperazinderivat mit stimulierender Wirkungsweise. Neben den im Vergleich zu anderen Piperazinderivaten eher milden stimulierenden Effekten scheint die Substanz auch beruhigend zu wirken, weshalb sie meist mit anderen Piperazinderivaten kombiniert wird um synergistische Effekte zu erzielen.

Methoxetamin ist ein Research Chemical, mit dissoziativer Wirkweise, das von der chemische Struktur Ketamin und PCP ähnlich ist. Im Vergleich zu Ketamin ist die Wirkung von Methoxetamin aber bei gleicher Dosierung intensiver, das Anfluten dauert erheblich länger und die Wirkung hält länger an. Da es sich bei Methoxetamin um ein Research Chemical handelt, gibt es nur wenige gesicherte wissenschaftliche Erkenntnisse über Risiken und Langzeitfolgen. Informationen über Dosierung, Wirkung und Risk Reduction beruhen hauptsächlich auf UserInnenberichten. Für dissoziative Anästhetika allgemein gilt, dass Mischkonsum mit Downern (Alkohol, Benzodiazepine, Opiate, GHB…) sehr riskant ist, da es zu Bewusstseins Verlust und Erbrechen kommen kann – eine Kombination die potentiell lebensbedrohlich ist. Viele UserInnen raten explizit vom Mischkonsum mit Alkohol ab. Der Mischkonsum von Methoxetamin und MDMA und MDMA-ähnlichen Substanzen birgt vermutlich besondere Risiken. Es ist ein Todesfall nach Mischkonsum mit MDAI bekannt geworden. Europaweit wurden bereits mehrere Todesfälle in Zusammenhang mit Methoxetamin-Konsum berichtet.

Paracetamol ist ein schmerzstillender und fiebersenkender Arzneistoff, der in vielen Medikamenten, die bei Erkältungsbeschwerden und grippalen Infekten eingesetzt werden, vorkommt.

Phenacetin ist ein Aminophenol-Derivat, welches bis 1986 zur Schmerzbehandlung und Fiebersenkung eingesetzt wurde. Wegen seiner krebserregenden und insbesondere nierenschädigenden Wirkung in Kombination mit anderen Schmerzmedikamenten wurde es aus dem Handel genommen. Phenacetin hat eine leicht euphorisierende und anregende Wirkung und wird vermutlich deshalb als Streckmittel eingesetzt[3].

pFPP (Fluorphenylpiperazin) gehört – wie mCPP und TFMPP – zur Gruppe der Phenylpiperazine. pFPP hat eine leicht euphorisierende Wirkungsweise und wurde deshalb - wie andere Piperazine auch – vermehrt als Inhaltsstoff von legal erhältlichen Freizeitdrogen (sogenannten „Party Pills") eingesetzt.

[2] Das Serotonin-Syndrom ist auf einen Überschuss an Serotonin zurückzuführen und äußert sich unter anderem in verschiedenen neuromotorischen und kognitiven Symptomen, wie z.B.: Ruhelosigkeit, rasche unwillkürliche Muskelzuckungen, gesteigerte Reflexbereitschaft, Schwitzen, Schüttelfrost und Tremor ein.

[3] http://www.saferparty.ch/download/file/Warnungen_PDF_2010/Kokain_Streckmittel_April_10(1).pdf

TFmPP (**Trifluormethylphenylpiperazin)** ist genauso wie mCPP ein Phenylpiperazin. Die Effekte von TFmPP ähneln jenen von MDMA, wobei die Wirkung stark dosisabhängig ist: Bei hohen Dosen reicht das Wirkspektrum in den halluzinogen Bereich (ähnlich Meskalin und Psylocibin).

Quellen: www.erowid.com; www.wikipedia.org; www.pharmawiki.ch; Trachsel, D.,Richard, N.: Psychedelische Chemie (2000), Nachtschattenverlag: Solothurn.

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Serotonin toxicity: a practical approach to diagnosis and treatment

Geoffrey K Isbister, Nicholas A Buckley and Ian M Whyte

ABSTRACT

- Excess serotonin in the central nervous system leads to a condition commonly referred to as the serotonin syndrome, but better described as a spectrum of toxicity — serotonin toxicity.
- Serotonin toxicity is characterised by neuromuscular excitation (clonus, hyperreflexia, myoclonus, rigidity), autonomic stimulation (hyperthermia, tachycardia, diaphoresis, tremor, flushing) and changed mental state (anxiety, agitation, confusion).
- Serotonin toxicity can be: mild (serotonergic features that may or may not concern the patient); moderate (toxicity which causes significant distress and deserves treatment, but is not life-threatening); or severe (a medical emergency characterised by rapid onset of severe hyperthermia, muscle rigidity and multiple organ failure).
- Diagnosis of serotonin toxicity is often made on the basis of the presence of at least three of Sternbach's 10 clinical features. However, these features have very low specificity. The Hunter Serotonin Toxicity Criteria use a smaller, more specific set of clinical features for diagnosis, including clonus, which has been found to be more specific to serotonin toxicity.
- There are several drug mechanisms that cause excess serotonin, but severe serotonin toxicity only occurs with combinations of drugs acting at different sites, most commonly including a monoamine oxidase inhibitor and a serotonin reuptake inhibitor. Less severe toxicity occurs with other combinations, overdoses and even single-drug therapy in susceptible individuals.
- Treatment should focus on cessation of the serotonergic medication and supportive care. Some antiserotonergic agents have been used in clinical practice, but the preferred agent, dose and indications are not well defined.

MJA 2007; 187: 361–365

With the introduction of numerous serotonergic agents in the past two decades, serotonin toxicity[1] has become an important and common adverse drug effect, which can be mild, moderate or even life-threatening. Serotonin toxicity can occur from an overdose, drug interaction or adverse drug effect involving serotonergic agents. Selective serotonin reuptake inhibitors (SSRIs) are one of the commonest groups of drugs taken in overdose,[2] and serotonin toxicity occurs in 15% of SSRI overdoses.[3] A growing list of medications has been associated with serotonergic toxicity; the drugs that have been clearly associated are given in Box 1. The potential for the development of serotonin toxicity is particularly important in patients being prescribed psychotropic medications, with an increasing proportion of the population taking the newer antidepressants.[4]

Serotonin toxicity results from an excess of serotonin (5-hydroxytryptamine [5-HT]) in the central nervous system (CNS), which can be due to several different pharmacological mechanisms. These include inhibition of the metabolism of serotonin (monoamine oxidase inhibitors), prevention of the reuptake of serotonin in nerve terminals (serotonin reuptake inhibitors), and increased serotonin precursors (tryptophan) or serotonin release (serotonin-releasing agents) (Box 2). The resulting excess CNS serotonin acts on serotonin receptors and produces the clinical effects. The exact role of the various serotonin receptors is not completely clear, but there is good evidence that the severe life-threatening clinical effects, such as rigidity and hyperthermia, are mediated by the 5-HT_{2A} receptors.[1,5]

Serotonin toxicity is sometimes called the serotonin syndrome, which is often used to refer to clinical effects "as defined by the Sternbach criteria".[6] However, these criteria were stated to be provisional, are non-specific and have never been validated (see **Diagnosis of serotonin toxicity**). The clinical features reported in the original description of the serotonin syndrome by Sternbach have often been taken as diagnostic criteria, which has led to some reported associations with medications that clearly do not cause serotonin excess. The atypical antipsychotic drugs, such as olanzapine, are a striking example. These have been reported as causing the serotonin syndrome,[7] despite having antiserotonergic actions. We contend that the diagnostic criteria developed more recently by our group — the Hunter Serotonin Toxicity Criteria[2] — are much more specific for serotonin toxicity.

Clinical features of serotonin toxicity

Serotonin toxicity is characterised by the presence of a triad of clinical features: neuromuscular excitation, autonomic stimulation, and changes in mental state (Box 3). There are a number of specific neurological signs that are not seen in many other conditions that should direct the clinician towards a diagnosis of serotonin toxicity. The most important is generalised hyperreflexia. Sustained clonus is usually found at the ankle; ocular clonus (or non-directional nystagmus) is also very common. Generalised spontaneous clonus may occur in moderate-to-severe cases, and is seen rarely in any condition other than serotonin toxicity.[2] The lower limbs usually have a much greater degree of hyperreflexia and clonus than the upper limbs[8] (although a mechanism for this consistent observation is not known).

Some mental state and autonomic features are also nearly always present, but have lower diagnostic utility, as they are indistinguishable from those observed with other causes of an agitated delirium. However, the presence of these features is often associated with moderate-to-severe serotonin toxicity.

Assessment of serotonin toxicity: diagnosis and severity

The assessment of serotonin toxicity requires determining, first, whether the clinical features are consistent with serotonin toxicity and, second, the severity of the toxicity. In patients with suspected serotonin toxicity, the clinical assessment should include observation for tremor, myoclonic jerks, diaphoresis, ocular clonus and

1 Drugs that have been associated with serotonin toxicity

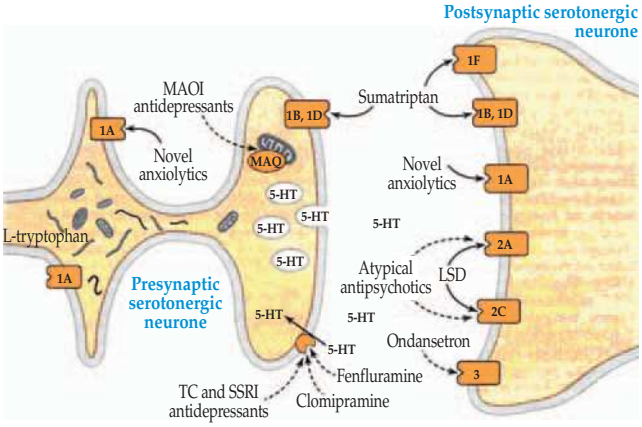
Serotonin reuptake inhibitors
- *Selective serotonin reuptake inhibitors:* fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram
- *Other antidepressants*: venlafaxine, clomipramine, imipramine
- *Opioid analgesics:* pethidine, tramadol, fentanyl, dextromethorphan
- St John's wort

Monoamine oxidase inhibitors
- *Irreversible monoamine oxidase A inhibitors:* phenelzine, tranylcypromine
- *Reversible monoamine oxidase A inhibitors:* moclobemide
- *Others:* linezolid

Serotonin-releasing agents
- Fenfluramine
- Amphetamines
- Methylenedioxymethamphetamine (MDMA; ecstasy)

Miscellaneous
- Lithium
- Tryptophan ◆

2 Pathways by which serotonin acts within the central nervous system, including serotonin reuptake transport, and metabolism of serotonin by monoamine oxidase



Solid-line arrows = agonist action; broken-line arrows = antagonist or inhibitor action. MAOI = monoamine oxidase A inhibitor; LSD = lysergic acid diethylamide; TC = tricyclic; SSRI = selective serotonin reuptake inhibitor; 5-HT = 5-hydroxytryptamine.

Adapted from: Frazer A, Hensler JG. Serotonin. In: Siegel GJ, Agranoff BW, Albers RW, et al, editors. Basic neurochemistry. Molecular cellular and medical aspects. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 1999. Reproduced with permission. ◆

agitation. Vital signs (heart rate, blood pressure and temperature) will usually be sufficient to diagnose autonomic features. However, most important is a focused neurological examination — mental state (eg, orientation, concentration, short-term memory); upper- and lower-limb tone, clonus and reflexes; and pupillary size, reaction and extraocular movements (opsoclonus). In most cases this is sufficient to make a confident diagnosis.[2]

Diagnosis of serotonin toxicity

A number of diagnostic criteria have been suggested for serotonin toxicity. The first and most commonly used are Sternbach's criteria.[6] Many of the 10 clinical features suggested as typical of serotonin toxicity by Sternbach are non-specific. These would also be commonly observed in many other conditions such as anticholinergic delirium, and alcohol and drug withdrawal states.[2] Sternbach's clinical definition was based on case reports and small published case series. Sternbach recognised that the features were non-specific and specified that other possible causes of the features must be excluded. Unfortunately, this caveat on the original description is almost routinely ignored. Thus, while Sternbach's criteria remain useful for early recognition, they cannot *by definition* be used in differential diagnosis.[1]

As the clinical features of Sternbach's criteria are not specific, they are also not useful for identifying new drugs as a cause of serotonin toxicity. Again, *by definition* they state that a *known* serotonergic drug must have been recently added or increased in dose. The folly of ignoring these two components of the syndrome definition is well illustrated by the fact that eight of the 10 "diagnostic" clinical features of the Sternbach serotonin syndrome are common features of the serotonin reuptake inhibitor discontinuation syndrome, and five are in the proposed diagnostic criteria for that syndrome.[9] In addition, eight of Sternbach's 10 "diagnostic" features can occur with catecholamine excess, and many features are found in other common toxidromes.

We recently developed diagnostic criteria for serotonin toxicity — the Hunter Serotonin Toxicity Criteria (HSTC) — by studying large numbers of patients ingesting serotonergic agents in overdose. The HSTC can be used to determine whether a patient who has taken an overdose has significant serotonin toxicity (Box 4).[2] As the HSTC were validated in the setting of a toxicology service where other drug-induced syndromes are frequent, the criteria are much more specific than Sternbach's criteria for features that solely relate to serotonin toxicity. Because they are more specific, the HSTC can be used for adverse drug reactions, but have not been validated for this purpose.

Differential diagnosis

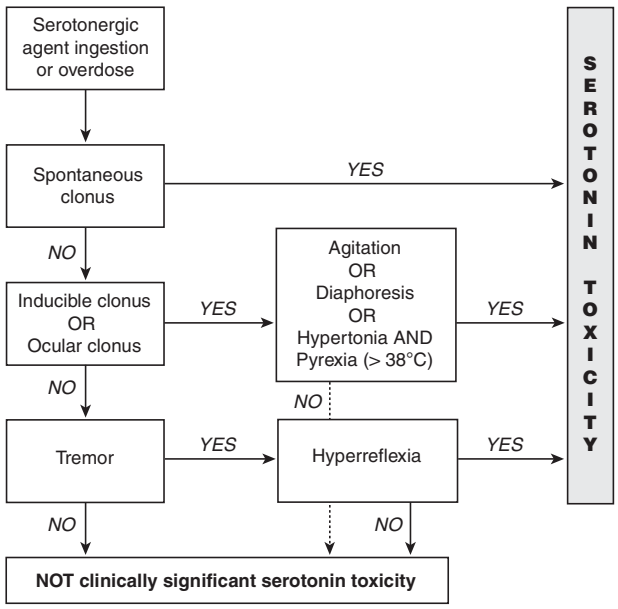
Although other adverse drug reactions can be initially mistaken for serotonin toxicity, a careful examination for specific neurological features, such as clonus, hyperreflexia and tone, makes it possible to distinguish other conditions. A list of differential diagnoses is given in Box 5. The most commonly confused neurotoxic syndrome is the neuroleptic malignant syndrome. However, neuroleptic malignant syndrome is associated with bradykinesia, lead pipe rigidity, and other extrapyramidal features, in contrast to the hyperkinesia, hyperreflexia and clonus seen with serotonin toxic-

3 Clinical features of serotonin toxicity

Neuromuscular effects	Autonomic effects	Mental state changes
• Hyperreflexia	• Hyperthermia: mild, < 38.5° C; severe ⩾ 38.5° C	• Agitation
• Clonus		• Hypomania
• Myoclonus		• Anxiety
• Shivering	• Tachycardia	• Confusion
• Tremor	• Diaphoresis	
• Hypertonia/rigidity	• Flushing	
	• Mydriasis	

◆

4 Flow diagram based on the Hunter Serotonin Toxicity Criteria[2]



ity. Neuroleptic malignant syndrome is also an idiosyncratic adverse drug reaction that has a more gradual onset and is not associated with overdoses of neuroleptics.

Non-convulsive seizures (toxic ictal delirium) may present as a severe fluctuating acute confusional state, which may be associated with autonomic features, hyperreflexia or occasional overt seizure activity. Although the many non-drug causes of non-convulsive status epilepticus (including most causes of encephalopathy)[10,11] must be excluded, drugs may induce this epileptic phenomenon, either dose-related or in withdrawal. The most common drug associations are with recently increased doses of phenothiazines and with benzodiazepine withdrawal.[12] It seems likely that some serotonergic drugs may also occasionally cause this syndrome. An electroencephalogram at the time is usually diagnostic, and rapid improvement with administration of benzodiazepines is usual. The latter may be the best way to clinically distinguish non-convulsive seizures from serotonin toxicity.[12]

Acute baclofen withdrawal (typically due to intrathecal pump failure) is a potentially life-threatening condition that presents with a raised temperature, autonomic instability and muscle spasms and rigidity.[13,14] The clinical features are difficult to distinguish from serotonin toxicity, but this rare diagnosis need only be considered in a few patients, and it should respond rapidly to reinstitution of baclofen. Interestingly, it has also been reported to respond to serotonin antagonists,[14] suggesting that it may even be a specific form of serotonin toxicity.

Severity of serotonin toxicity

The spectrum of serotonin toxicity can be roughly divided into three groups of severity based on the requirement for medical intervention:

- ***Mild serotonergic features.*** These may or may not interfere with the patient and may occur with therapeutic use of many serotonergic agents.
- ***Moderate toxicity.*** Symptoms cause the patient significant distress and deserve symptomatic treatment.
- ***Severe serotonin toxicity or serotonin crisis.***[1] This is characterised by a rapidly increasing temperature associated with muscle rigidity, and will progress to multiorgan failure if not treated within hours. This is a medical emergency and is almost exclusively associated with combinations of drugs acting at different sites, most commonly including a monoamine oxidase inhibitor and an SSRI.[15]

A similar division was also suggested by Radomski and colleagues, labelled as mild serotonin toxicity, serotonin syndrome, and toxic states.[16] A number of other scoring systems have been suggested; for example, a serotonin toxicity scale devised by Hegerl and coworkers for depressed patients taking paroxetine.[17]

Serotonin toxicity occurs in three main settings. Adverse reactions to normal therapeutic doses usually only cause mild-to-moderate toxicity. Overdose of a single serotonergic agent typically leads to moderate toxicity only. Nearly all severe serotonin toxicity relates to drug interactions (which may also occur in overdose).

There are a number of different mechanisms by which the drugs associated with serotonin toxicity (Box 1) cause excess serotonin. As mentioned above, severe serotonin toxicity mostly occurs with combinations of drugs (most commonly an SSRI and a monoamine oxidase inhibitor) acting at different sites.[15] Patients who ingest any combination of serotonergic drugs in overdose must be observed carefully. However, not all combinations cause increased toxicity. For example, although methylenedioxymethamphetamine (MDMA; ecstasy) can cause serotonin toxicity, SSRIs do not appear to increase serotonergic effects from such serotonergic amphetamines and may reduce neurotoxicity.[18,19]

That single agents are unlikely to cause severe serotonin toxicity has been confirmed in studies of overdose patients ingesting SSRIs alone.[2,3] In one study of SSRI overdoses, serotonin toxicity occurred in 15% of cases, but there were no severe cases.[3]

Treatment

Treatment for all forms of serotonin toxicity is supportive care and cessation of any serotonergic medications. Severe serotonin toxicity or serotonin crisis is a medical emergency and initial manage-

5 Differential diagnoses for serotonin toxicity

Differential diagnosis	Distinguishing features
Neuroleptic malignant syndrome	Absence of neuromuscular excitation;* and presence of bradykinesia, lead-pipe rigidity, and extrapyramidal features
Non-convulsive seizures	Electroencephalogram features, and response to benzodiazepines
Acute baclofen withdrawal	History of intrathecal baclofen pump, and response to baclofen
CNS infection — encephalitis, meningitis	Absence of neuromuscular excitation*
Anticholinergic delirium	Absence of neuromuscular excitation,* bowel sounds absent, and dry skin
Sympathomimetic toxicity	Absence of neuromuscular excitation*
Malignant hyperthermia	Anaesthetic exposure, and absence of neuromuscular excitation*

* Hyperreflexia, clonus and myoclonus.
CNS = central nervous system. ◆

ment must focus on airway, breathing and circulation. Supportive care, including passive and active cooling of the patient, sedation, intubation and muscle paralysis, must take precedence over any specific pharmacological treatment. Hyperthermia and muscle rigidity appear to be the most important effects, and this supportive care can prevent secondary complications, such as rhabdomyolysis, renal failure and disseminated intravascular coagulation.

Serotonin toxicity may progressively increase over a number of hours after ingestion of implicated drugs. Patients who have moderate serotonin toxicity should be observed for a period of 6 hours; however, if a slow-release formulation has been ingested, such as venlafaxine, observation should be continued for 12 hours. It is appropriate to provide symptomatic treatment for these patients, including benzodiazepine sedatives, antiemetics and specific pharmacological therapy. Most patients will improve within 24 hours of ceasing the serotonergic medication.

There may be a role for specific serotonin antagonists in serotonin toxicity, and animal studies provide data that non-specific HT_2-antagonists and more selective 5-HT_{2A}-antagonists reverse the lethal effects of serotonin toxicity.[5] There are numerous case reports of patients improving after being given serotonin antagonists.[20-24] However, it is difficult to separate these "responses" from the natural resolution of toxicity. There are no controlled trials demonstrating their effectiveness and further study is required. Cyproheptadine and chlorpromazine are the HT_2-antagonists that have been used most extensively,[20,23,25] and have a long history of safe use for other medical conditions. Oral cyproheptadine (4–12 mg) is probably the most useful 5-HT_2 antagonist for moderate toxicity. Its main side effect is sedation, which is usually beneficial. However, as cyproheptadine can only be administered orally, it is unlikely to be effective in patients administered activated charcoal, and has limited use in severe toxicity. In severe serotonin toxicity, chlorpromazine may be more appropriate to use for sedation than other routine sedative agents. It can cause hypotension, so patients must receive sufficient volume loading. Other non-selective 5-HT_2 antagonists, such as the atypical antipsychotics, may be effective,[21,22] but there is far less experience with their use.

In patients who ingest overdoses of serotonergic agents, there are a few additional considerations. The selective use of activated charcoal may be warranted, but only if it can be given within an hour. Early risk assessment should also consider the possibility of interacting drugs, and non-serotonergic toxic effects (eg, QT prolongation with citalopram).[26]

Some individuals appear to be more susceptible to mild-to-moderate serotonin toxicity, but it is unclear whether this usually has a pharmacokinetic (eg, decreased drug metabolism) or pharmacodynamic (eg, serotonin receptor polymorphism) explanation.[27] A great deal of research would be needed to enable identification of such individuals before treatment. Until then, prevention of serotonin toxicity is as simple (or as difficult) as avoiding prescribing serotonergic drugs. However, we believe that avoiding monoamine oxidase inhibitors may be sufficient to prevent life-threatening toxicity. It also makes sense to us to generally minimise the use of serotonergic drugs used for non-psychiatric conditions.

Competing interests

None identified.

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