Academic Student Paper: Why Alprazolam (Xanax) is an essential and indispensable life-saving drug for patients suffering from rare diseases

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Abstract

Since the market launch of alprazolam (in many countries under the brand name Xanax), this highly potent benzodiazepine has had a disastrous public reputation. Even in media, entertainment and pop culture, its very powerful effects have made it emblematic of a sinister psychodrug that drags its users into an abyss of dependence and suffering. Indeed, the substance has certain specific properties (mood elevating, extremely fast acting, very short half-life, effects on adrenaline), but at its core it is a benzodiazepine like any other. How Xanax came to be demonized is therefore an important question to be discussed. On the other hand, the substance alprazolam possesses a unique property that is hardly known even among experts to this day and can be life-saving for people whose body's own adrenaline synthesis and regulation is disturbed by certain (often hereditary, auto-immune, or toxic) rare diseases. For these patients, there is virtually no other medication available than alprazolam, which quickly, specifically and highly effectively inhibits pathological adrenaline surges, for example due to disorders of the SAM axis, effectively at the site of adrenaline (epinephrine) synthesis by up to 50%. Logically, this also gives rise to the legendary reputation that alprazolam is more effective than any other benzodiazepine, especially in patients with panic disorders. This paper, a source-supported opinion piece, is intended to remind the worldwide community of medical professionals that alprazolam is a legitimate, and often the only available, treatment option for abnormal adrenaline balance involving the adrenal gland and/or the SAM axis. Demonizing alprazolam in a clinically well regulated setting is therefore immoral and detrimental to the patients health and compliance.

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Academic Opinion Paper

Why Alprazolam (Xanax) is an essential and indispensable life-saving drug for patients suffering from rare diseases

Abstract

Since the market launch of alprazolam (in many countries under the brand name Xanax), this highly potent benzodiazepine has had a disastrous public reputation. Even in media, entertainment and pop culture, its very powerful effects have made it emblematic of a sinister psychodrug that drags its users into an abyss of dependence and suffering. Indeed, the substance has certain specific properties (mood elevating, extremely fast acting, very short half-life, effects on adrenaline), but at its core it is a benzodiazepine like any other. How Xanax came to be demonized is therefore an important question to be discussed. On the other hand, the substance alprazolam possesses a unique property that is hardly known even among experts to this day and can be life-saving for people whose body's own adrenaline synthesis and regulation is disturbed by certain (often hereditary, auto-immune, or toxic) rare diseases. For these patients, there is virtually no other medication available than alprazolam, which quickly, specifically and highly effectively inhibits pathological adrenaline surges, for example due to disorders of the SAM axis, effectively at the site of adrenaline (epinephrine) synthesis by up to 50%. Logically, this also gives rise to the legendary reputation that alprazolam is more effective than any other benzodiazepine, especially in patients with panic disorders. This paper, a source-supported opinion piece, is intended to remind the worldwide community of medical professionals that alprazolam is a legitimate, and often the only available, treatment option for abnormal adrenaline balance involving the adrenal gland and/or the SAM axis. Demonizing alprazolam in a clinically well regulated setting is therefore immoral and detrimental to the patients health and compliance.

What is alprazolam (Xanax)?

Alprazolam belongs to the group of drugs known as benzodiazepines and, with its market launch in the 1980s, is one of the younger and highly potent class of these substances, which became known worldwide through the first drug belonging to this group, diazepam ("Valium"). Initially very welcome as a substitute for the much more dangerous barbiturates, the always advisable restriction to the lowest possible daily doses and narrowly defined indications was neglected by most physicians at that time. This group of drugs, which is still frequently prescribed, has a strong sedative and anxiety-relieving (anxiolytic) effect. The substance class enhances the effect of an inhibitory nerve messenger (GABA) in the brain. As a result, the nerve cells are less excitable - a calming and anxiety-relieving effect becomes apparent.[1-5]

Alprazolam is characterized by a particularly strong effect and a short half-life. At the same time, the drug is accused of having a higher addictive potential, although this has never been proven without contradiction. All benzodiazepines have a potential for addiction, especially in people who are predisposed to it. However, this also applies to a wide range of other substances as well, such as pregabalin, SSRIs, SNRIs and other psychotropic drugs, without demonizing them. For some of these blockbusters of the pharmaceutical industry, even the terms “addiction” and “withdrawal symptoms" have been replaced by the artificial PR term "discontinuation syndrome”, just as if this would be any better. While more expensive drugs like pregabalin (mentioned as pars pro toto) has at no point in time proven beyond reasonable doubt to relieve anxiety better than benzodiazepines, not to mention the infamous but epidemically prescribed selective serotonin reuptake inhibitors (SSRIs), it is clinically highly relevant whether a drug produces the desired effect after 45 minutes (alprazolam) or 45 days (SSRIs), if at all. It is completely undisputed that alprazolam is highly effective against acute anxiety and especially against panic attacks. Why it is so massively effective at this, unlike other benzodiazepines, was unclear for some time.

By the time research took a new look at the substance and highly interesting pharmacological characteristics were discovered, the 1990s had already dawned and the pharmaceutical industry had new money printing machines on the market with the patented, expensive SSRIs (Prozac and its siblings), which supposedly made it possible for the first time for every general practitioner to safely treat depressed and anxiety-ridden patients themselves without a referral to a psychiatrist and allegedly without the risk of addiction and with a good conscience. The fact that these promises were never kept and that endless numbers of patients have to struggle with severe side effects, even today, long-term damage, deaths and dependence issues caused by SSRIs, SNRIs and other supposedly "more harmless" substances, remains to this day as a problem outside the general perception. Alprazolam, however, which had even been registered as having an additional mood-enhancing effect, was an unpleasant alternative to the new wonder-world of Prozac and all the selective inhibitors of serotonin and noradrenaline.

So, no one had any interest in investigating the unique properties of alprazolam. No scientist touched the topic after the mid 1990ies. The SSRI/SNRI marketing campaign ran hot, and science no longer received funding for further research into Xanax, especially since the patent protection (meaning high yields) would have come to an end anyway. So, instead, alprazolam became an orphan itself, demonized as a cheap drug for the poor. However, alprazolam was and is one of the very few pharmaceuticals that has been scientifically proven to reduce the body's own adrenaline synthesis and release in a credible, observable and measurable way. This effect is achieved within minutes and in doses that are virtually free of serious side effects. For patients with a diseased adrenal gland or other biological reasons for uncontrollable adrenaline (epinephrine),

alprazolam (Xanax) is still to be considered a first line treatment with few side-effects and controllable discontinuation patterns.

Stress hormones and their importance

In addition to the nervous system, the hormone balance represents the second important communication network of the body. The pituitary gland is responsible for the majority of the body's hormone secretions, which in turn is controlled by the hypothalamus, located in the diencephalon, as the higher-level control center. The pituitary gland can be divided into anterior and posterior lobes, with the anterior lobe acting as a hormone gland and the posterior lobe as a hormone reservoir. It is connected to the hypothalamus via the infundibulum (pituitary stalk). Control by the hypothalamus proceeds via two pathways: first, the long axons of special hypothalamic neurons extend via the infundibulum into the posterior pituitary lobe, where they release hormones - in some cases directly into the blood. Other hypothalamic neurons activate a vascular system in the infundibulum with their messenger substances, which passes into another vascular network in the anterior pituitary lobe, which regulates hormone production there. The perception of stress in the brain is transferred into physiological stress reactions of the organism via different hormonal axes. The main function of the two most important axes is to increase the readiness to perform, but they act through different patterns: The sympathetic-adrenal-axis, SAM) mediates rapid active responses of target organs and tissues or the organism (fight-or-flight) by means of (in this case, peripheral) adrenergic and noradrenergic neurons and represents excitatory, motor-emphasized activity as well as what can be called neuronal pathwaying, differentiation plus far-reaching stabilization effects in the CNS. Among other things, it dominates in situations that are perceived as controllable, acceptable, or positive. The hypothalamic-pituitary-adrenal axis (HPA axis) puts the body into a 'state of emergency' somewhat delayed and mediates stress adaptations in areas such as metabolism and the immune system via various hormones, primarily cortisol.

It has an inhibitory and destabilizing effect on the CNS is significantly involved in the pathophysiological developments in long-term stress. Acute stress arises primarily from the perception of an acutely threatening situation, e.g., shock, attack, psychosocial stressors (conflict, testing), pain or fear triggers, but also physical stress such as extreme physical exertion or hypoglycemia. The sensory signals are classified as threatening in the neocortex or directly and more rapidly by the limbic system, which then stimulate the locus caeruleus in the brainstem within fractions of a second - partly with the involvement of the hypothalamic hormone CRH - which simultaneously functions as the center of noradrenergic activity in the CNS and the control center of the sympathetic nervous system. This control does not occur directly, but via pathways radiating into the periventricular hypothalamus, from where the sympathetic nervous system is stimulated, and the body is physiologically placed in a state of excitation or alarm. The adrenal medulla - activated by the sympathetic nervous system - supports this process by releasing the hormones adrenaline and noradrenaline.

Stress response mediated by norepinephrine enables the body to react quickly and powerfully, particularly through an increased supply of oxygen, glucose, and free fatty acids, as well as increased alertness and responsiveness. Energy sources are mobilized, skeletal muscles and cardiovascular system are stimulated for physical performance, and vital functions are secured. According to Cannon (already in 1929), this sympathetic response is called the fight-or-flight response because it takes all precautions in the organism so that it can physically defend itself optimally in stressful situations or bring itself to safety. Also released by the adrenal gland’s medulla, body-own opioids simultaneously facilitate

stress management by inhibiting pain as well as sensory-emotional 'background noise'.

The hypothalamic-pituitary-adrenocortical axis (HPA) represents, along with the sympathetic-adrenal medullary axis, the most important endocrine stress axis, but - activated by largely the same stressors - it becomes active with a delay compared to the SMA and therefore also has a particular effect during long-term stress. If a perception or situation is qualified as stressful by the cortex and especially the limbic system, they stimulate - via serotonergic and cholinergic fibers - the release of the signal peptide CRH (corticotropin-releasing hormone) in the hypothalamus, which on the one hand activates the SNA, which on its part, however, essentially corresponds to the activity of the locus caeruleus. In addition, CRH plays a role as a neurotransmitter in the hippocampus and amygdala, among others, in mediating stress and anxiety responses

In its main function, however, CRH activates the synthesis and release of ACTH (adrenocorticotropic hormone) in the anterior pituitary. Agonistic factors in this process include adrenaline, ADH, and various inflammatory mediators such as TNF-a and interleukin-1. ACTH, in turn, causes the release of glucocorticoids, especially cortisol, from the adrenal cortex via the bloodstream. Cortisol and ACTH regulate the further release of CRH through negative feedback. In addition, with persistent cortisol secretion, the glucocorticoid receptor GR, to which cortisol docks, is downregulated. In the case of permanent stress, in addition to other pathophysiological processes, defects in the negative feedback loop apparently play an essential role, so that the physiological decrease in CRH and cortisol levels no longer occurs. Like the neurotransmitters of the SAM, all substances involved in the HPA axis also have a psychotropic effect. Since CRH, in addition to its action as a releasing hormone, also modulates CNS stress responses as a neurotransmitter, it is also referred to as a neuropeptide and thus an intermediate form between neurotransmitters and hormones. CRH is not only stimulated neuronally, but also via messenger substances such as angiotensin II or certain cytokines (inflammatory mediators). In addition to cortisol and ACTH, opioids, stress and CRH-BP (CRH-binding proteins), which is formed near the hypothalamus, also have inhibitory effects on CRH. Cortisol also has an agonistic effect on GABAergic neurons, which in turn inhibit CRH neurons. Thus, the stress response is self-limiting in several respects (2-3 hours apart), provided the inhibitory systems are intact. In addition, somatostatin and the 'anti-stress and caring hormones' prolactin and oxytocin inhibit the HPA axis at all regulatory levels. Most of the effects of HPA activity are based on cortisol. It can reach up to values tenfold above the normal plasma concentration in stressful situations and ensures that additional energy reserves are activated for higher performance in addition to the SAM effect. As a fat-soluble hormone, it can - unlike adrenaline, for example - pass through the cell membrane and activate genes intracellularly via specific protein receptors (e.g. for the new synthesis of glucose) or suppress them (e.g. to inhibit excessive stress reactions). In fact, increased cortisol concentration - which has a time-delayed onset compared with adrenaline - has an agonistic effect on adrenergic stress responses in the short term, but a suppressive effect after a limited action phase. When HPA inhibition is impaired or emotional balance is permanently disturbed, cortisol levels remain elevated. Such can also be seen in socially subordinate animals as well as in humans with enduring psychosocial stress, fear or depression. In post-traumatic stress disorder, on the other hand, there is a drop in cortisol. The main cortisol effects include: Gluconeogenesis, hyperglycemia, release of amino and fatty acids through protein and fat breakdown, inhibition of protein synthesis and tissue anabolism, e.g. in skin, collagen, vessels and bones (long-term: osteoporosis), inhibition of immune cells (proliferation, activity) and inflammatory mediators such as interleukins, interferon or

histamine (decreased resistance) , decreased release of sex hormones, b-endorphin, CRH, ACTH and in the CNS: inhibition of memory, information processing, sexuality, sleep as well as neuronal pathway, connectivity and differentiation. Until today, stress reactions and stress perception are commonly regarded as something burdensome, even per se pathogenic, which must be overcome and avoided as if it were a disease. Most people would immediately define stress avoidance as an important goal. However, this is countered by the physiological significance of the stress reaction, which on the one hand represents a vital adaptive capacity of the organism to cope with physical and/or emotional stressors in the short term and to actively overcome - or, if need be, to endure - a stressful situation. On the other hand, stress, insofar as it is associated with the active initiatory accomplishment of tasks and acted out, possesses stimulating properties without which a shaping of life or the development of personality, relationships, initiatives and ideas would not be possible. A clear physiological distinction must be made here between the noradrenergic-adrenergic stress response, which focuses more strongly on impulsivity, extraversion, and control over short episodes, and the cortisol-emphasized long-term stress response (HPA axis) to more endurable, immobilizing stressors without the possibility of prompt resolution.[9-14]

The evaluation of a stressor is also crucial - unconsciously by the limbic system on the one hand, and via conscious qualification of the situation. A parachute jump, a strong acute stressor, will give a different sign to the physiological stress reaction than a traffic accident. Similarly, most people would not think of emotionally associating running a marathon with a court case, falling in love with anger, or preparing for a wedding for three months with a serious illness, even though these events are primarily mediated by the same stress-associated systems of the body. Therefore, even identical events such as parachute jumping, wedding preparation, a change in life, or a severe ordeal under identical conditions can be evaluated in extremely opposite ways by different people, eliciting fear, helplessness, curiosity, a sense of control, or pleasure, depending on the "omen." However, when appraised positively or classified as controllable, the stressor mediates primarily stabilizing effects in the CNS via the noradrenergic system, including neural pathway and differentiation processes and improved learning and memory. The so called "noradrenergic response" (involving the noradrenergic system as well as the sympathetic-adrenal medullary axis) does not lead to feelings of helplessness and returns to normal physiological levels after the stressor is removed.[20,22,23]

In contrast, helplessness, i.e., the evaluation as uncontrollable, activates the HPA system and thus the cortisol-emphasized (long-term) stress, thereby reducing the activating effects of the stress response and leading in the long run to desensitization with pathological changes and permanent emotional imbalance. This reaction is favored by external factors such as loss of social competence (e.g. job loss), psychosocial conflicts (partnership, family, workplace, friends) and lack of psychosocial support. Often, then, the very idea and expectation of stressful situations sustains the stress response. In the CNS, the HPA system acts antagonistically to the noradrenergic system: there is inhibition of neuronal differentiation and activity, degeneration of neuronal connections. Nevertheless, this is not in principle a catabolic, pathological process: various authors drew attention to the fact that, on the one hand, especially the limbic and cortical neurons, which are particularly sensitive to cortisol, degenerate even in the absence of cortisol action (e.g. in animal experiments after removal of the adrenal cortex) and even require small amounts of the hormone for regeneration. On the other hand, it is precisely the softening of entrenched pathways and behaviors by higher glucocorticoid exposure over time that enables changes and solutions that would not have been possible if earlier patterns had been maintained. Thus, in

animal experiments, under permanently high cortisol levels, it was primarily behaviors that were "unlearned" that were unsuitable for successful termination of the stress-response process. Therefore, it is the destabilization and dissolution of patterns, networks and connections in the case of unresolved stresses and situations that can lead to a solution.[1-19]

Adrenal stress in rare diseases

Everything mentioned before is crucial and 'explosive' in patients who suffer (as a main or secondary effect of their disease) from a pathological disorder of the SAM axis or a pathological release of stress hormones. If this is the case, neither "stress reduction" nor none of the normally recommended changes of lifestyle will be an appropriate solution. Most physicians are only aware of a direct biologically driven overproduction of adrenaline from adrenal tumors, which can be surgically removed. Almost completely absent from the textbooks are dozens of rare diseases (aka "orphan diseases") of which many lead to irregular and usually excessive adrenaline secretions, most commonly in a wave-like pulse secretion pattern with an elevated baseline value. Often without psychological reason, but destroying the whole balance of the previously described stress axes.[20-24]

In such quite dangerous cases "classical" treatments like counseling, psychotherapy etc. have approximately the effectiveness of a philosophical conversation with a house owner about the unbearable heat in his house while in the boiler room in the basement of the house the water heater heats up due to defective sensors, leading to steam related damages in the infrastructure until, finally, the house will burn into ashes.

Since this observation is to some extent also partly applicable to cortisone release, is it extremely difficult to determine outside of controlled clinical studies, which of the many hormones and pathways involved is the (most) affected one. These systems are highly complex leading to quite dramatic dysfunctions which remain elusive in diagnostics but with severe consequence for the patient. From high blood pressure to a breakdown of the entire stress regulation system, heart attacks, heart damage, heart failure, strokes, dementia, behavioral disorders, anxiety, panic-like states, (malignant) sleep disorders, an elevated risk of accidents, depression-like mood, manic behavior, delusions, violence, self-injury, eating disorders, total exhaustion, manias, sleep syndromes, seizure disorders, way up to tragic suicides are real-life can be real life consequences.

Psychologizing these biologically induced symptoms further exacerbates the suffering of these patients by adding to their destructive illness the burden of "working on it long-term" in counseling or psychotherapy. The families of those affected are often told most of the same psychological "wisdoms", which further increases the pressure of suffering. This is not to say that stress-related adrenaline spikes are not treatable with psychotherapy per se - but only as long as a rare organic disease is not the root cause. As banal as this may sound, even in the year 2022 this important and fundamental differentiation is not yet common knowledge in medicine.

Everything just mentioned applies to people who do not suffer from a pathological disorder of the SAM axis or a pathological release of stress hormones. If this is the case, neither "stress reduction" nor a change of lifestyle or even psychotherapy will help. The overwhelming majority of physicians knows about an overproduction of adrenaline only in the context of adrenal tumors (e.g. pheochromocytoma), which can be surgically removed. Almost completely absent from the textbooks are the dozens of rare "orphan diseases" that lead to irregular, idiosyncratic and mostly excessive adrenaline pulses/secretions. Often without any psychological reason, but destroying the whole balance of the previously described stress axes. "Classical" treatments like psychotherapy have approximately the effectiveness of a philosophical conversation

with a house owner about the unbearable heat in his house, while in the boiler room the water heater heats up due to defective valves and pipes until the house explodes with a loud bang.

Since the adrenaline level of the human organism is, to a large extent also directly connected to cortisone, it is extremely difficult to measure it accurately outside of controlled clinical studies. This leads to a situation that even dramatic dysfunctions remain elusive with dire consequences for the patients. From high blood pressure to breakdown of the entire stress regulation, heart attacks, strokes, dementia, behavioral disorders, anxiety, panic-like states, (malignant) sleep disorders, accident risks, depression, manic behavior, delusions, violence, self-injury, eating disorders, total exhaustion, manias, aggressive REM-sleep syndromes, seizure disorders up to suicides and many other sequelae can and will be the direct consequence.[1,6,9,14,16,21,22,24]

Psychologizing these organically induced symptoms further exacerbates the suffering of the affected patients by adding to their destructive illness the entirely useless burden of "working on it long-term." The families of those affected are then told most of the same psychological nonsense, which further increases the pressure of suffering which, as a secondary consequence triggers additional psychological stress. In one line: never ever treat a patient psychologically until you are absolutely certain that his/her “panic” is not caused by biological issues. This is not to say that emotion-induced adrenaline spikes do not exist or were not treatable psychotherapeutically - but only as long as a rare organic disease is not the true reason. As simple as this may sound, even in 2022 this important and fundamental differentiation is by far still not common knowledge in medicine.[20-24]

Severe and most severe disorders of the SAM and HPA axes are seen often in rare, autoimmune and/or toxic diseases, but remain unnoticed due to the huge lack of knowledge of the entire medical profession which does not even have easy-to-perform tests available, with the aforementioned dramatic health and social consequences for the sufferers.[3,7,9,12,11,13,17,18,19]

Limited treatment options: Never forget that Xanax (alprazolam) can be a first line treatment

To the astonishment of many laymen, there are hardly any useful "adrenaline stoppers" or "epinephrine/adrenaline blockers" on the market. The best known ones are

- clonidine
- guanfacine
- lofexidine
- methyldopa
- guanabenz

and all of them are as ineffective as they have side effects in inflammatory changes of the relevant sections of the adrenal glands or other sensitive sites of the SAM axis. What remains is that substance whose name is in the title of this paper: Xanax, i.e. the unfairly demonized substance alprazolam. For it is precisely this alprazolam which, in addition to its mode of action typical of benzodiazepines, reduces the synthesis of adrenaline by up to 50%. In addition, it seems to bring the entire adrenaline axis into balance a good deal. This also explains its significantly better effect in panic attacks compared to all other benzodiazepines, which do not affect adrenaline synthesis and its pathways.[15]

Thus, alprazolam is an indispensable drug in the field of rare diseases and should be carefully become rehabilitated as a highly potent and beneficial drug with some serious undesired effects, such like most other psychotropic medical drugs.

Any physician who has a reasonable suspicion that his or her patient has symptoms suggestive of non-pyschologically induced excessive or deranged adrenaline levels takes moral blame if he or she does not attempt therapy with alprazolam (Xanax) in appropriately effective doses.[15]

Of course, only after informed consent of the patient and under strict supervision. A possible abuse as a "downer" is rarely or almost never observed in people suffering from rare diseases. In addition, such a suspicion could easily be detected with simple drug level tests in the course of a laboratory examination.

Summary

Alprazolam is the drug of first choice for the treatment of hyperadrenalism or SAM axis dysfunction in patients with rare diseases (“orphan diseases”).

Conflicts of interest

None declared.

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