Apunts Med Esport. 2018;53(198):55–61

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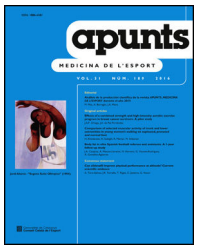

ORIGINAL ARTICLE

Bipolar disorders and comorbid conditions – Ethical considerations in sports☆

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Received 26 August 2017; accepted 16 October 2017
Available online 21 December 2017

KEYWORDS
Bipolar disorder;
Comorbidities;
Sports;
Ethics;
Doping violation;
World Anti-Doping Code, prohibited list, and therapeutic use exemptions;
Psychopharmacology;
Hypothetical cases;
Education;
Clinical care

Abstract
Introduction: The goal of pharmacologic intervention is therapeutic outcome – maximal efficacy with minimal adverse effects. In treating bipolar disorder, this may be complicated by comorbidities and/or adjunctive medications required to address adverse effects. Optimal rational polypharmacy may maximize therapeutic outcome yet could create ethical issues in competitive sports. The World Anti-Doping Code (WADC) and yearly published World Anti-Doping Agency Prohibited List are intended to deter and sanction athletes using performance-enhancing agents while promoting an even playing field for all competitors. This paper presents three hypothetical examples (ADHD/lithium-tremor/pain) wherein unintended Prohibited List contravention would result in doping violation disqualifications without approved Therapeutic Use Exemptions (TUEs).
Method: Hypothetical case analyses with literature review.
Results: Comorbid ADHD – the Prohibited List precludes psychostimulants (methylphenidate/amphetamines) in competition (S6) but permits guanfacine/atomoxetine. When psychostimulants effectively treat ADHD in athletes with bipolar disorder but guanfacine/atomoxetine do not, these patient-athletes, with clinician's certification and supportive documentation, should file TUEs.

Lithium-tremor – beta-blockers are frequently prescribed to control lithium-tremor but are not permitted for specific sports (P2). If alternatives (primidone) are ineffective, TUEs are indicated.

☆ Presented in part at the 19th Annual Conference of the International Society of Bipolar Disorders, Washington DC, May 4–7, 2017.

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https://doi.org/10.1016/j.apunts.2017.10.001

Pain – chronic pain management is difficult in athletes as narcotic analgesics (S7) and cannabinoids (S8) are prohibited in competition. When comorbid pain is not controlled with approved medications, TUEs are required.
Conclusion: Patient-athletes with bipolar disorder and comorbidities require holistic approaches with appreciation of both the WADC and Prohibited List. Athletes should list all medications with diagnoses/obtain TUEs/verify proposed medication status (banned/restricted/permitted) with appropriate International Federations and/or Olympic organizations. Clinicians should be cognizant of these issues when treating patient-athletes.

PALABRAS CLAVE
Trastorno bipolar;
Comorbilidades;
Deportes;
Ética;
Violación de la norma antidopaje;
Código mundial antidopaje;
Lista de Sustancias Prohibidas, y
Exenciones por uso terapéutico;
Psicofarmacología;
Casos hipotéticos;
Educación;
Cuidados clínicos

Trastornos de bipolares y comorbilidades – consideraciones éticas en deportes

Resumen
Introducción: El objetivo de la intervención farmacológica es el resultado terapéutico: máxima eficacia con mínimos efectos adversos. Esto resulta difícil a la hora de tratar el trastorno bipolar, debido a las comorbilidades y/o fármacos complementarios necesarios para abordar los efectos adversos. La polifarmacia racional óptima puede maximizar el resultado terapéutico, aunque podría crear cuestiones éticas en los deportes competitivos. El Código Mundial Antidopaje (WADC) y la Lista de Sustancias Prohibidas de la Agencia Mundial Antidopaje, publicada anualmente, tienen como objetivo disuadir y sancionar a los atletas que utilicen agentes para mejorar el rendimiento, y promover un marco de igualdad para todos los competidores. Este documento presenta tres ejemplos hipotéticos (TDAH/temblor secundario al litio/dolor) en los que la contravención no deliberada de la Lista de Sustancias Prohibidas derivaría en descalificación por violación de la norma antidopaje sin aprobación de las Exenciones por Uso Terapéutico (TUEs).
Método: Análisis de caso hipotético con revisión de la literatura.
Resultados: TDAH Comórbido – la Lista de Sustancias Prohibidas excluye los psicoestimulantes (metilfenidato/anfetaminas) en la competición (S6) pero permite guanfacina/atomoxetina. En los casos en que los psicoestimulantes constituyeran un tratamiento eficaz para el TDAH en los atletas con trastorno bipolar, a diferencia de guanfacina/atomoxetina, estos pacientes-atletas deberán presentar TUEs, junto con la certificación y documentación de respaldo del clínico.

Temblor secundario al Litio– a menudo se prescriben beta-bloqueantes para controlar el temblor secundario al litio, pero que no están autorizados para deportes específicos (P2). En caso de que los fármacos alternativos (primidona) resulten ineficaces, serán necesarias las TUEs.

Dolor – el manejo del dolor crónico es difícil en atletas, ya que los analgésicos narcóticos (S7) y cannabinoides (S8) están prohibidos en la competición. Cuando el dolor comórbido no se controla con fármacos autorizados, son necesarias las TUEs.
Conclusión: Los pacientes-atletas con trastorno bipolar y comorbilidades precisan enfoques holísticos, con reconocimiento tanto del WADC como de la Lista de Sustancias Prohibidas. Los atletas deberían realizar un listado de todos los fármacos incluyendo diagnósticos/obtener TUEs/verificar el estado de la medicación propuesta (prohibido/restringido/permitido) con las Federaciones Internacionales adecuadas y/u Organizaciones Olímpicas. Los clínicos deberán ser conocedores de estas cuestiones a la hora de tratar a los pacientes-atletas.

Introduction

Bipolar disorders are classified as a severe mental illness with a lifetime prevalence of 4.4% in the United States and 2.4% worldwide.[1,2] A recent meta-analysis addressing prevalence in primary care noted a current prevalence of 3.7%.[3] Bipolar disorders are associated with significant medical and psychiatric comorbidities,[4] have a disproportionate global disease burden,[5] and are frequently complicated by suicidal behaviors.[6,7] Thus, early diagnosis with pharmacologic interventions is key to the long-term outcome for patients with bipolar disorders.

The goal of pharmacologic intervention in both research trials and clinical care is therapeutic outcome – maximal efficacy with minimal adverse effects.[8] In treating bipolar disorders, this may be complicated by comorbidities and/or adjunctive medications required to address adverse effects. Optimal rational polypharmacy may maximize

therapeutic outcome yet could create ethical issues in competitive sports.

The World Anti-Doping Code (WADC)[9] and yearly published World Anti-Doping Code Prohibited List[10] are intended to deter and sanction athletes using performance-enhancing agents while promoting an even playing field for all competitors. Criteria for including substances in the Prohibited List are outlined in WADC Section 4.3.1:

''4.3.1 A substance or method shall be considered for inclusion on the Prohibited List if WADA, in its sole discretion, determines that the substance or method meets any two of the following three criteria:

4.3.1.1 Medical or other scientific evidence, pharmacological effect or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or enhances sport performance;
4.3.1.2 Medical or other scientific evidence, pharmacological effect or experience that the Use of the substance or method represents an actual or potential health risk to the Athlete;
4.3.1.3 WADA's determination that the Use of the substance or method violates the spirit of sport described in the introduction to the Code.''[9]

The key word in Section 4.3 is ''potential'' and the Prohibited List refers to ''and other substances with a similar chemical or biological effect(s).''[9,10] As such, numerous substances not on the Prohibited List may meet these criteria. This is especially pertinent to bipolar disorders with comorbid conditions wherein psychotropics frequently are used off-label.[11,12] Further, substances that were once monitored or considered ''related'' have been advanced to the Prohibited List.[13] Since there is strict liability for doping violations, it is incumbent on athletes to list all substances and, as indicated, to obtain a Therapeutic Use Exemption (TUE).[14] Criteria for obtaining a TUE include:

''4.1 An Athlete may be granted a TUE if (and only if) he/she can show that each of the following conditions is met:

a. The Prohibited Substance or Prohibited Method in question is needed to treat an acute or chronic medical condition, such that the Athlete would experience a significant impairment to health if the Prohibited Substance or Prohibited Method were to be withheld.
b. The Therapeutic Use of the Prohibited Substance or Prohibited Method is highly unlikely to produce any additional enhancement of performance beyond what might be anticipated by a return to the Athlete's normal state of health following the treatment of the acute or chronic medical condition.
c. There is no reasonable Therapeutic alternative to the Use of the Prohibited Substance or Prohibited Method.''[14]

This paper presents three hypothetical examples in the treatment of bipolar disorders with comorbidities (comorbid ADHD, lithium-induced tremor, and comorbid pain) wherein unintended Prohibited List contravention would result in doping violation disqualifications without approved TUEs.

Method

Hypothetical case analyses with literature review.

Cases

ADHD

A 19-year-old female elite gymnast was referred to a child study team in elementary school for marked inattention and following comprehensive assessment was diagnosed with ADHD-inattentive. The parents declined standard psychostimulants. Atomoxetine had limited benefit and maintenance guanfacine resulted in decreased, but not resolved, ADHD features. At age 14, she had a first major depressive episode which remitted with a 7-month outpatient fluoxetine treatment course. At age 15, she developed hypomanic features followed by a recurrent major depressive episode which was effectively treated with lamotrigine 100 mg qhs. She was formally diagnosed with Bipolar II Disorder and ADHD. With a recurrent hypomanic episode at age 16, lurasidone 40 mg qdinner was effectively added to her lamotrigine. At this time, her parents agreed to substitute psychostimulants for the guanfacine to maximize control of ADHD symptoms with all ADHD symptoms resolved on methylphenidate-XR 18 mg qam. There have been no recurrent bipolar or ADHD symptoms for the past 3 years. As an elite athlete, she requested documentation from her pediatrician and psychiatrist as she filed a TUE to enable continued treatment with methylphenidate which is a prohibited (S6) substance in competition.

Lithium tremor

A 25-year-old male elite archer was first psychiatrically hospitalized and diagnosed with Bipolar I Disorder following a manic episode with psychotic features at age 13 that responded to haloperidol with divalproex sodium. Thereafter, he developed a post-manic depressive episode with suicidal behavior which was effectively treated with divalproex sodium and lamotrigine. This combination was not effective for maintenance therapy in spite of dose titrations with therapeutic drug monitoring for he had further recurrent psychiatric admissions – 2 manic episodes and 3 depressive episodes – before the age of 20. Each depressive episode was associated with suicidal behavior. Additional psychotropic trials with oxcarbazepine, quetiapine, aripiprazole, and lurasidone all worked for acute episodes only. At age 20, he agreed to initiate lithium and has remained stable without any further episodes or subclinical symptoms at lithium 900 mg total daily dose with a lithium blood level of 0.55 mEq/l. He had comorbid polysubstance dependence (alcohol and benzodiazepines) in his early teens now in chronic remission. Lithium treatment course was complicated by a new-onset dose-dependent tremor. To minimize this tremor, lithium was titrated down from a maximum 1350 mg total daily dose (level 0.95 mEq/l) to the current maintenance dose. Neither primidone (titrated to 125 mg bid) nor gabapentin (titrated to 300 mg tid) further improved this tremor and topiramate caused word-finding difficulties;

however, his tremor totally resolved with propranolol 40 mg bid. As an elite athlete, he requested a TUE to enable continued treatment with propranolol which is a prohibited (P2) substance in archery.

Pain

A 33-year-old female cyclist was first diagnosed with Bipolar I Disorder during a psychiatric admission for a manic episode at age 18. She was effectively treated with divalproex sodium but discontinued this secondary to weight gain following which she was readmitted at age 20 for a second manic episode. During this second admission, comorbid intermittent explosive disorder was diagnosed. To control both conditions while minimizing enzyme induction impacting her birth control medication, oxcarbazepine was initiated and titrated to 600 mg bid maintenance dose with resolution of further bipolar and anger features. Her key comorbid medical conditions were progressive osteoarthritis in bilateral knees and left elbow and a chronic pain syndrome s/p surgical repair of her left forearm following a training accident. Initial treatments included glucosamine, chondroitin, and acetaminophen with prolonged exercise to which topical/oral NSAIDs were added to better control her pain. Over time, these treatments were not sufficiently effective to permit continued competition requiring progression to tramadol and thereafter oxycodone. With combined prolonged exercise, NSAIDs, and low dose oxycodone, she had limited pain and was able to return to prior elite performance levels. The addition of cannabinoids further diminished her pain with associated reduction in opiate usage. As both narcotic analgesics (S7) and marijuana (S8) are prohibited in competition, she appropriately pursued a TUE with assistance from her medical team.

Discussion

These hypothetical cases are unique and permit the development and discussion of key points in bipolar disorder, comorbid conditions, pharmacotherapy, and ethical considerations in sports as outlined in the WADC.

First, early-onset bipolar disorder has been associated with comorbid alcohol/substance dependence, comorbid anxiety, increased suicidal behaviors, and increased depressive severity all consistent with potentially poorer prognosis supporting the need for early diagnosis and intervention.[15]

Second, the significant degree of comorbid psychiatric conditions with bipolar disorders is often underestimated. Recent literature addressing prevalence rates for bipolar disorders and comorbid psychiatric conditions notes: >40% for any anxiety disorder,[16] >20% for ADHD,[17] and >20% for alcohol and substance use disorders.[18,19] Presence of comorbidities may vary based on population age and setting with increased psychiatric comorbidities reported in pediatric bipolar disorder (>60% for anxiety disorders; >40% for ADHD).[6] Further, in a national survey ($N = 34,653$), 19.71% of those with anger had comorbid bipolar disorder and >60% of bipolar disorder depressed patients in a small study had anger attacks.[20,21] These prevalence rates emphasize the need for clinicians to appreciate that bipolar disorder patients are at high risk for specific comorbid psychiatric disorders, to consider these conditions both at time of initial diagnosis and longitudinally, and to address pharmacologic interventions that may serve to treat multiple disorders.

Third, bipolar disorder pharmacotherapy requires minimization of adverse effects, especially in specific populations at risk. These populations include but are not limited to: women in child bearing years, pregnancy, patients with renal/hematopoietic/liver diseases, patients with comorbid medical and psychiatric conditions requiring minimal metabolic induction, patients with metabolic syndrome or family history of metabolic disorder, patients with history of drug reactions (Steven Johnson Syndrome), and geriatrics.

Fourth, suicidal behaviors (suicidal ideation, suicide attempt, and suicide) are a major concern in the illness course and treatment of bipolar disorders. Specifically, suicidal ideation has been reported in ~50% and suicide attempts in ~25% of bipolar patients, respectively, with a standardized mortality ratio for suicide of >20-fold than in the general population.[6,7,22,23] Since suicide is the cause of death in 15–20% of all bipolar patients,[24] treatment requires consideration of suicide prevention strategies. Multiple randomized controlled trials and meta-analyses report the significant anti-suicidal properties of lithium in mood disorders (suicide odds ratio of 0.13 compared to placebo[25]; lithium treatment with an 80% decrease in all suicidal acts with decreased lethality of acts[26]; lithium maintenance discontinuation with 20-fold increased risk of suicidal acts during the first year off lithium[27]).

Fifth, there is limited research addressing prevalence rates for psychiatric disorders among athletes, with no studies specifically addressing bipolar disorders.[28] A small sports psychiatrist survey ($N = 40$) noted the preferential use of lamotrigine for bipolar disorders.[29] Sports and exercise are considered important for both physical and mental health wellbeing with improved quality of life measures, increased socialization and decreased stigma[30,31]; however, whether exercise is an appropriate treatment for bipolar disorder has been questioned and requires further research.[32]

Sixth, ethical considerations in sports require that all athletes adhere to the WADC with emphasis on the Prohibited List and obtaining TUEs as indicated. When obtaining a TUE, two questions need to be considered: (a) if the athlete has been stabilized with a prohibited medication for a severe illness or associated comorbidity, should that athlete be mandated to try an approved drug with a prior history of inferior response; (b) should in-competition prohibited medications be acutely discontinued for a given competition? The three cases address these points.

Seventh, psychostimulants (methylphenidate and mixed amphetamine salts) are preferential first-line treatments for ADHD followed by non-psychostimulants (atomoxetine and guanfacine).[33,34] Psychostimulants are prohibited substances in competition (S6) whereas both atomoxetine and guanfacine are approved.[10] In the ADHD case presented, atomoxetine was not effective and guanfacine had only partial benefit leading ultimately to successful treatment with methylphenidate-XR. Without obtaining a TUE, the WADC would require the gymnast either to take the historically inferior atomoxetine/guanfacine during competition or not take methylphenidate during competition. In the first instance the gymnast's ADHD would be only partially treated and in the second instance the ADHD would remain

untreated with neither upholding the WADC goal of creating an even playing field.[9] Competitive gymnasts must be attentive to avoid unnecessary, but costly, scoring deductions; consider that deductions can occur for each failure to present (acknowledge the panel judge) before and/or after an exercise (0.30), for not beginning an exercise within 30 s of being signaled by judge or green light (0.30), for inappropriate attire (0.30), and for each overtime exercise (0.10).[35] As criteria are met (4.1a, 4.1b, 4.1c), a TUE is indicated for this case.[14]

Eighth, beta-blockers (propranolol) and primidone are preferential first-line treatments for essential tremor (Class A) followed by gabapentin (B), topiramate (B) and other lower level evidenced-based interventions.[36,37] Beyond dose reduction for lithium-induced tremors, with limited research studies, pharmacotherapies for lithium tremor mirror recommendations for essential tremor.[38] Beta-blockers are Prohibited Substances both in-competition and out-of-competition for archery (P2) whereas primidone, gabapentin, and topiramate are approved.[10] In the lithium-tremor case, lithium dose reduction diminished the tremor severity without increased subclinical inter-episode symptoms.[39] Primidone, gabapentin and topiramate trials were not effective and benzodiazepines were avoided due to his history of polysubstance dependence. His lithium-induced tremor resolved with propranolol; however, without a TUE, he would be required to change his mood stabilizing agent as the other recognized treatments for this tremor had all been ineffective. This case is a classic example of poor prognosis – early-onset with comorbid substance dependence and suicidal behaviors. Within 7 years, there were 7 distinct episodes (3 manic and 4 depressive) including 4 suicide attempts. Numerous pharmacotherapies (3 anticonvulsants and 3 second generation antipsychotics individually, in combination, and with dose titrations) were effective for acute episodes only. With lithium maintenance, he had been stable for 5 years without further suicidal behaviors. In consideration of the significant bipolar-suicide literature, to request this athlete to change psychotropics would be contraindicated and could be life threatening with both increased suicidal behaviors and lethality of acts.[26,27] As criteria are met (4.1a, 4.1b, 4.1c), a TUE is indicated for this case.[14]

Ninth, pain management is a complex issue balancing the need to decrease pain severity with both its negative impact on HRQoL[40–43] and its significant inter-relationship with mental health[44–47] while avoiding excessive interventions that might lead to dependence. With increased pain severity associated with disease progression, pain management may evolve from non-pharmacologic, to non-opiate pharmacologic, to opiate, to potential adjunctive cannabinoids, and even surgical treatments. The case described, osteoarthritic pain with a chronic post-trauma pain syndrome, is an example of treatment evolution to manage persistent pain. There are several unique aspects to this case. Oxcarbazepine in rodent models is noted to have a synergistic analgesic effect with both acetaminophen and NSAIDs.[48,49] Tramadol, though a weak opioid with addictive properties, is not a Prohibited Substance but rather listed as part of the Monitoring Program[50] – as such, tramadol is still approved for use by athletes.[51] As narcotic analgesics are Prohibited Substances in competition (S8),[10] the cyclist would not be permitted to use oxycodone which controlled her pain without a TUE; however, the cyclist had followed general guidelines for non-pharmacologic and non-narcotic pharmacologic pain control such that use of oxycodone should be permitted.[52] Further, to minimize total narcotic analgesic dosing with the ultimate intent to switch from oxycodone back to tramadol, the cyclist added cannabinoids which is also a Prohibited Substance in competition (S9).[10] Recent literature suggests that cannabinoids are beneficial in the treatment of chronic non-cancer pain including arthritis where in animal models it may modify disease progression suggesting that cannabinoids potentially could be used as treatment for the underlying disease process.[53,54] As criteria are met (4.1a, 4.1b, 4.1c), a TUE is indicated for this case.[14]

Future research needs include: (a) prevalence rates in athletes of specific psychiatric illnesses, such as bipolar disorder, where there is a paucity of data[28]; (b) evidenced-based studies addressing whether athletes with specific psychiatric diseases when treated with a Prohibited Substance receive any performance enhancement (consider stimulants in ADHD); (c) evidenced-based studies determining if a Prohibited Substance beyond treating symptomatically can also modify disease progression (consider cannabinoids for pain in arthritis); (d) national and international data on which psychotropics are used for specific psychiatric diseases among athletes; (e) well-designed studies to determine the therapeutic benefit of exercise and sports for patients with bipolar disorders.[32]

The principal strength and limitation of this paper relates to the use of hypothetical bipolar disorder cases. With such cases, it is possible to develop complex presentations permitting a greater understanding of the illness process (comorbidities, prevalence, suicidal behaviors, treatment adverse effects) from which step-wise treatment options can be suggested for both the patient's wellbeing and safety in the context of the WADC. Yet hypothetical cases cannot be generalized and do not represent what decisions would be reached by the TUE Committee (TUEC) of a given National Anti-Doping Organization[14] in real cases or whether national TUEC decisions would be consistent. It is important to assess real cases with decisions to have a better understanding as to what degree sport authorities recognize the health needs of the athlete. The clinician must always remember that the athletes are patients first and the WADC is not the arbiter of their health.

Conclusions

Patient-athletes with bipolar disorder and comorbidities require holistic approaches with appreciation of both the WADC and Prohibited List. Specifically, a physician's primary responsibility is the health, well-being, and safety of all patients, including patient-athletes. A secondary consideration pertinent to patient-athletes is the use of pharmacotherapies on the Prohibited List – this may be required based on the complexity of individual cases. An example from the hypothetical cases was the need for lithium treatment in a complex bipolar patient with a history of multiple suicide attempts as a means to maximize both mood stabilization and minimize any suicidal

behaviors with resultant lithium-tremor that was responsive only to propranolol.

Athletes should list all medications with diagnoses, verify proposed medication status (banned/restricted/permitted) with appropriate International Federations and/or National Olympic Committees to avoid inadvertent doping violations, and obtain TUEs where indicated. Clinicians should be cognizant of these issues when treating patient-athletes, review all medications with possible implications for the Prohibited List, and, where indicated, assist with requested documentation.

Conflict of interest

There are no conflicts of interest to declare.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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