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Elephant in the room? The methodological implications for public health research of performance-enhancing drugs derived from the illicit market

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'All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.'[1]

Background

In a recent issue of this journal Graham *et al*.[2] reported on the analysis of 57 oral, injectable and percutaneous performance-enhancing drugs (PEDs) obtained from the illicit market in the United Kingdom. They found significant levels of adulteration and misbranding: some drug products contained different active pharmaceutical ingredients (APIs) from those listed on the labelling (for example, testosterone propionate was substituted for nandrolone decanoate, which exhibits significantly different pharmacokinetics and pharmacodynamics)[3–8] whereas others had no detectable APIs as per the analyses undertaken. To our knowledge this is the first published piece of work from the UK providing analytical evidence of the high level of adulteration of a sample of PEDs for more than 14 years.[9] It serves to advance the contemporary evidence base from a collection of anecdotes and informal observations. Further, it broadly supports the findings from convenience samples[9–12] and case reports[13,14] in other settings both temporally and spatially†.

> Q. What's the difference between an anthropologist and an epidemiologist? A. The anthropologist thinks that the plural of anecdote is ''data''.[15]

It is reasonable to infer from these data,[2,9–14] as well as information from genre publications[16–26] and the user community,[27–29] that adulterated PEDs are likely to be commonplace on the illicit market. However, in order to obtain a detailed understanding of the prevalence of these tainted products and the forms of adulteration that affect them, not only is comprehensive forensic analysis of the drug products required (going beyond identification and occasionally quantifying the strength of APIs) but the sampling work needs to employ methods that control for both random error (ensuring adequate power) and bias (particularly selection bias).[30] Probability sampling is unlikely to be technically feasible in this setting[31] but the issue of selection bias can largely be addressed through the use of sampling frames that better represent the structure and function of the illicit market(s); these will need to be non-reactive and take into account the relative importance of different drugs and specific drug products, manufacturers, distribution networks and memes (the latter being the cultural diffusion of the practices and trends in relation to the use of PEDs).[16–18,32–34] Moreover, drug testing and analysis also need to be undertaken in studies where possible associations between the use of PEDs and adverse events are being examined.

Why is any of this important? From our perspective the failure to better understand and quantify the issue of adulteration better could be one issue – of many – that confounds the analysis of the adverse events that have been 'associated'[35–37] with PED use, leading to specious reasoning when undertaking causal inference. Specifically, if the composition of the drug products cannot be assured and we do not quantify and assess the impact of this, then how can we know if we are examining the effects of a specific drug product?

Adulteration and the Illicit Market

Drawing from definitions in law[38] along with related standards, rules and guidance,[39,40] PEDs intended for use in humans that are not based on sufficient quality management that is required for drug/medicinal products[39–41] should be seen as adulterated[38] – because they are not based on the cornerstone

† Although noting that the methodology of the analyses undertaken in one study[9] and the case reports[13,14] were not adequately described.

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of '*quality, safety and efficacy*'.[42] This hypernym subsumes the phenomena of substandard[43] and counterfeit[44] drugs. The adulteration may be either unintentional or intentional.

To date a limited number of small-scale studies examining this issue in PEDs have found: the substitution of API(s) from that stated on the labelling/packaging (including progesterone and tocopherol instead of the anabolic steroid methenolone enanthate);[11] the inclusion of undeclared APIs;[2,9,11–14] no detectable APIs as per those stated on the labelling/packaging and as per the analyses undertaken;[2,9] and, APIs that are under[9,10,13] and over strength.[9,14] There is therefore an additional need to systematically examine the prevalence and forms of adulteration that affect these drug products as a whole, i.e. the API(s) and excipient(s), and the relationship therein,[45] as well as quantifying any contamination, be this biological, chemical or with foreign matter. This latter issue of contamination is particularly important with PEDs given that many dosage forms are injectable and used in high volume often over long periods of time.[46]

Contemporary data suggest that the majority of users obtain their PEDs from the illicit market[47–51] and although some users do obtain drug products through prescription[47–49,51] (few data are available on the proportion of these that would be considered clinically appropriate based on current guidelines), or over the counter (see below), the illicit market is the sole source of some drug products that are in high demand by users. Indeed, in high-income countries many anabolic steroids used in 'stacking' – one of the central tenets of anabolic steroid use[52] – have either been discontinued/are not licensed (particularly some of the oral 17-α alkylated products such as methandienone/'Dianabol'), or are only licensed for veterinary use (such as boldenone undecenoate).

Although detailed empirical data are lacking, there appear to be three sources of products that comprise the illicit PED market, which given its proscribed nature should be viewed heuristically:

- Products purportedly manufactured legitimately (typically) in middle-income countries, including China, Egypt, India, Mexico, Pakistan, some former Eastern Bloc countries (including Russia) and Thailand, where regulatory oversight and enforcement is weak,[53,54] which may place them at risk of adulteration.
- Products manufactured and/or packaged in clandestine 'underground labs' of varying capacity and quality,[18,23,55–57] where, because they exist outside of the drug regulatory system, the products cannot demonstrate sufficient 'quality, safety and efficacy'[42] *de jure,* so they must be classed as adulterated.[38] It is important to note that some of these labs appear to manufacture products that include counterfeit versions of legitimate, licensed, drug products, as well as their own 'generic' and 'proprietary' products, which do not necessarily appear to fit within the World Health Organization's definition of a counterfeit drug.[44]
- Legitimate products manufactured in high-income countries that are: purchased over the counter (which includes sales over the Internet) in countries where this practice is lawful or where regulatory oversight and enforcement is weak;[53,54] diverted to the illicit market through theft;[58–60] unlawfully resold;[61] or prescribed/dispensed as a result of fraud.[49,62]

The proportion that each source contributes to the market as a whole is not known (and the task of quantifying this is made all the more difficult because there is no easy way to check the bona fides of the supply chain and drug products). Moreover, it is reasonable to assume that the contributions that each source makes are likely to be both temporally and spatially dynamic as a result of, *inter alia,* different policies pursued between (and within) nation-states towards restricting the supply, demand and use of these drugs, which will subsequently result in varying degrees of action by law enforcement and drug regulatory authorities; the demand for specific drug products by the user community; and, wider economic and social policies, including globalization,[63,64] '. . . consumerism, the explosion of free trade and communication across borders, and increasing use of the internet. . .'[63]

The Implications for Public Health Research

Many of the data on the adverse events associated with PED use are derived from case reports/series and cross-sectional study designs that are observational in nature. Observational approaches are likely to remain the mainstay of our research designs for some time (however, even adequately powered prospective cohort studies seem unlikely). This is, at least in part, due to the methodological, ethical and logistical constraints, which apparently preclude the use of randomized controlled trials that make use of the high-dose polydrug regimens that are common within this community.[52] It is imperative, therefore, that we pay particular attention to variables that could affect the internal validity of any work before it is undertaken.[65–69]

Data from studies have demonstrated some discordance between self-reported use of anabolic steroids and that detected through urinalysis.[70,71] Whether this discrepancy is unintentional[72–76] or intentional on behalf of the patients/participants is unclear. However, it is apparent that self-reported drug use cannot be relied upon (a finding not limited to this group).[77–79] Moreover, the relatively small number of studies that have performed drug qualitation (typically urinalysis for anabolic steroid use) have not systematically performed drug quantitation nor examined the composition (including strength of APIs) of the drug products being used by the patients/participants.

While difficulties in implementing such drug testing and analysis procedures are evident, we contend that these methodological limitations have weakened the internal validity and, subsequently, the generalizability of much of the observational work in this field. The analytical data and related information that are available clearly suggest that forms of adulteration that affect the APIs of drug products are likely to be commonplace[2,9–14,16–29] (however, as noted above, data on the composition of the drug product as a whole will also be critical to advancing our understanding of the pharmacological actions and, subsequently, any adverse events mediated by these drugs). These findings are supported by the discordance between the specific drug products/APIs reported by users and those detected (or metabolites thereof) by urinalysis[70] (although we cannot rule out the possibility that some of the participants in this study set out to intentionally deceive the researchers over the APIs of the drug products). Moreover, the issue of adulteration is likely to increase for the foreseeable future if the popularity of these drugs increases,[80] coupled with their ease of availability through transnational Internet sites purportedly trading in these products.[63] While we are not aware of any systematic, representative, studies examining the sale of PEDs on the Web, illustrative searches using the terms 'buy anabolic steroids'[81] and 'buy growth hormone'[82] provide an indication of the prevalence and global nature of such sites; with recent data from relatively large Internet-based studies (n = 1955[51] and n = 500[48]) in the United States reporting that between 52.7%–79.4% of these

participants had purchased anabolic steroids over the Internet (although it is unclear how representative these groups are).

Likewise, the issue of drug testing and analysis in our studies has become more salient given the veritable cornucopia of dietary, herbal and sports supplements as well as 'lifestyle/wellbeing' drugs available on the legitimate and illicit markets. This is not only because of the co-occurrence of adverse events following the use of some of these products,[83–86] but also that some products have been adulterated with APIs such as anabolic steroids (for example, methandienone and stanozolol),[73–76] centrally acting appetite suppressants (for example, sibutramine and rimonabant),[87,88] diuretics (for example, bumetanide and furosemide)[88–90] and drugs for erectile dysfunction (such as tadalafil),[91] or even openly, albeit unlawfully, marketed as containing clenbuterol[92] (a β_2 agonist) and dinitrophenol (an uncoupler of mitochondrial oxidative phosphorylation)‡.[93] Moreover, some of these APIs were found to be present at high strength[73–76,87,90–93] (not all reports provided data on this parameter). This, along with the use of off-the-shelf 'designer steroid' supplements[76,94–101] – which are marketed as safe(r) and legal alternatives to 'classical' anabolic steroids – have the potential to confound the data if we do not systematically quantify the use and composition (along with any adulteration) of these products in both users and 'control groups'.

There is a paucity of evidence on a wide range of issues in relation to the use of PEDs. While the work by Graham *et al*.[2] has contributed to our understanding of the role of adulterated drug products, there is a scant scientific evidence base that can inform drug-prevention or harm-reduction interventions in relation to the adverse events that have been associated with the use of these drugs. Indeed, without the inclusion of this key scientific element, the credibility of any public health interventions for those using PEDs – a culture characterized by immense amounts of contradictory information and where 'change agents' and 'opinion leaders'[33] (such as 'steroid gurus') often have financial conflicts of interests – will remain compromised. In 1997 Gary Ferenchick suggested that urinalysis to identify use of anabolic steroids should be used in research studies simply because self-reported drug use could not be relied upon.[70] Today, more than 12 years later, we echo these views and, further, argue that comprehensive drug testing and analysis must become an integral component of our research. Tackling this 'elephant in the room' can best be served through meaningful dialogue, debate and collaboration across the diverse disciplines and specialities working in this field. Only then will we be better placed to examine the (mis)use of PEDs and any association with adverse events.

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‡ References[88,89,91,93] are press releases or reports from national drug/food regulatory authorities

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