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An unhealthy glow? A review of melanotan use and associated clinical outcomes

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ABSTRACT

Aim: Socio-cultural emphasis on having a tan has led to blackmarket diversion of synthetic-tanning products Melanotan I and II. This review of literature on clinical outcomes of Melanotan I and II aims to present extant literature on synthetic-tanning and its range of effects.
Methods: A review was conducted according to The Critical Appraisal Skills Programme (CASP). A database search was conducted to identify relevant publications. Clinical trials and clinical case presentations relating to melanotan use were included. Publications not in English and with a lack of specificity to the topic were excluded.
Results: The review yielded eighteen clinical trials and twenty-one clinical case presentations. Side effects observed include nausea, darkening of existing naevi and yawning. Systemic toxidrome and melanoma have also been evidenced. Potential harms include bloodborne virus, infection and contaminated and mislabelled products. Shortcomings in clinical reporting have limited determinations of causality in diagnoses.
Conclusion: Side effects observed in clinical trials are largely minor. Long-term health outcomes are as yet undocumented. Much of the harms related to melanotan use are associated with online sourcing of unregulated products. A systematic approach to clinical case reporting is needed in melanotan associated adverse health outcomes. The counterfeit PIEDs market and polypharming practices amongst users must be considered in reports of harm.
Implications: This review makes recommendations to inform enhanced clinical responses, and has underscored the need for future Internet and clinical research to investigate prevalence and user profiling, and to map health outcomes in melanotan users.

1. Introduction

Contemporary individual, social and cultural values placed on aesthetic ideals to conform to the '*cult of the body beautiful*' have fuelled '*health marketability*', popularity and diffusion of image enhancement drugs via under the counter and web sources (Brennan, Van Hout, & Wells, 2013; Evans-Brown, McVeigh, Perkins, & Bellis, 2012). Westernised values attribute tanned skin to beauty, success and health, and have encouraged public consumerism to avoid UV exposure known to cause premature ageing and carcinogenesis, in favour of the use of sunless-tanning agents (Evans-Brown, Dawson, Chandler, & McVeigh, 2009; Evans-Brown et al., 2012; Hadley & Dorr, 2006). These agents are synthetic analogues of the endogenous melanocortin peptide hormone alpha-melanocyte stimulating hormone (α-MSH) and were first synthesised in the 1980s for photoprotective effects (Langan, Nie, & Rhodes, 2010). This paper focuses on the health consequences and clinical outcomes of melanotan clinical trials and clinical case presentations. Desirable, minor, chronic and acute side effects of melanotan use are identified.

1.1. Background

At present, three main formulations, Melanotan I (afamelanotide), Melanotan II, and bremelanotide, exist. Afamelanotide, the first regulated a-MSG analogue, stimulates melanogenesis (pigmentation of the hair and skin in mammals) by heightening the production of eumelanin (O'Leary, Diehl, & Levins, 2014). Research continues on its use for vitiligo, solar urticarial, polymorphous light eruption, and prevention of squamous cell carcinoma and actinic

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keratoses in photosensitive subjects and organ-transplant recipients (O'Leary et al., 2014). Since afamelanotide was developed in the 1980s, a surge in demand for sunless-tanning agents has resulted in the marketing of multiple unregulated a-MSH analogues (Evans-Brown et al., 2009, 2012; O'Leary et al., 2014). Melanotan I was the first of these unregulated analogues with reported structure similar to afamelanotide, and with names often used interchangeably (Evans-Brown et al., 2009, 2012; McVeigh, Evans-Brown, & Bellis, 2012). Another synthetic analogue of α-MSH called Melanotan II has since emerged, and whilst it increases pigmentation at lower cumulative doses than Melanotan 1, higher levels of side effects relating to effects on satiety for weight loss and sexual stimulation are reported (Mahiques-Santos, 2012; Mataix, 2012). Melanotan I and II are more than 1000 times more potent than endogenous a-MSH (Hadley & Dorr, 2006; Langan et al., 2010). Bremelanotide is the third available variation of Melanotan II and was specifically designed for sexual stimulation (Evans-Brown et al., 2009).

Synthetic analogues of α-MSH are not illegal to use, possess or import, but domestic sale and supply outside of clinical trials is legislated in the UK and other countries. Of concern, however, is that these products (commonly injected) sold to the public are unregulated and untested (Evans-Brown et al., 2012), sold without prescription, potentially contaminated (Breindahl et al., 2015), counterfeit and with contents unverified (McVeigh, Evans-Brown, & Bellis, 2012) and also occurring in other image enhancement compounds (Kimergård, McVeigh, Knutsson, Breindahl, & Stensballe, 2014).

1.2. Identified concerns

1.2.1. User groups

Studies collecting demographics on tanners have found females to be more likely to engage in tanning behaviours (Harrington et al., 2011; Lostritto et al., 2012; Petit, Karila, Chalmin, & Lejoyeux, 2014), however, both females and males use melanotan (Hope et al., 2013; Van Hout & Brennan, 2013). Cultural ideals of health (Glassner, 1990), gender and sexual attractiveness (Lynch, 2012) have initiated the transgression of melanotan use from subcultural groups such as bodybuilders and sex workers (Mahiques-Santos, 2012; Van Hout & Brennan, 2013) to the general population.

1.2.2. Authenticity and nature of sourcing

Sourcing of melanotan largely occurs through web retailing by unregulated vendors (Evans-Brown et al., 2012). Sourcing routes are commonly identified through online information exchange between users (Van Hout, 2014).

1.2.3. Health risks

Very little is known about long-term outcomes of use (Mahiques-Santos, 2012) despite reporting of adverse reactions such as episodic nausea and vomiting, cardiac conditions, collapse, fatigue, hypertension, facial redness, blood and skin infections (Brennan et al., 2013; Van Hout & Brennan, 2013) and clinical concerns relating to increased skin pigmentation, rhabdomyolysis, systemic toxicity with sympathomimetic symptoms, renal dysfunction and reversible encephalopathy syndrome (Brennan et al., 2013; Evans-Brown et al., 2012; Javed, Yarrow, & Hemmington Gorse, 2013).

Although the risk of bloodborne virus is lower for performance and image enhancing drug (PIED) users than for other injecting drug user groups (NICE, 2014), online normalisation of unsupervised use and self-experimentation (Van Hout, 2014) to include polypharming (Van Hout & Brennan, 2013) supports the adaptation of injecting risk behaviours and high risk tanning behaviours (Langan et al., 2010). Potential for dependence has been noted by researchers (Evans-Brown et al., 2009; Mahiques-Santos, 2012; Mataix, 2012; McVeigh, Evans-Brown and Bellis, 2012) and some indicators of dependence have been noted in a single case study (Van Hout & Brennan, 2013).

1.2.4. Danger to regulatory regimes/law enforcement

Unauthorised routes to retail promote consumer anonymity and supplier protection (Kimergård et al., 2014) and have resulted in great difficulties in estimating manufacture of products, prevalence of use and vendor supply chains (O'Leary et al., 2014).

1.2.5. Public health responses to date

Public health responses have been primarily reactive in attempting to curb unauthorised supply channels via the internet, tanning and beauty salons, gyms, and cosmetic physicians (Langan et al., 2010; Mahiques-Santos, 2012), and medical responses within the clinical setting (McVeigh, Evans-Brown and Bellis, 2012). Targeted health education efforts are hampered by a rise in '*short cut*' beauty consumerism and the immediately salient nature of tanned skin (Brennan et al., 2013; Mahiques-Santos, 2012). In research, recent efforts to understand this form of image enhancement drug use have focused on engaging with melanotan user forums and user case studies (Van Hout & Brennan, 2013; Van Hout, 2014).

This review is intended to further our knowledge on the issue of health consequences of synthetic-tanning and aimed to present the extant literature base pertaining to Melanotan I and II use and associated clinical outcomes. In order to achieve this, a review of literature, pertaining to melanotan clinical trials, and clinical case presentations of melanotan use were conducted.

2. Methodology

A comprehensive review of the literature was conducted to identify clinical trial research, and clinical case presentations, in relation to Melanotan I and II. Bremelanotide was excluded from the literature search as it is less commonly used in the general population. Due to the specificity of the research topic, systematic review was according to The Critical Appraisal Skills Programme (CASP) guidelines (Public Health Resource Unit, 2006). The CASP is widely used and provides a comprehensive system for assessing quality of the literature chosen for the purpose of review. The Critical Appraisal Skills Programme (CASP) uses specific tools to rigorously assess the quality of studies using various research designs, developed from research conducted by the Evidence Based Medicine Working Group published in the *Journal of the American Medical Association* (Public Health Resource Unit, 2006). These tools were developed to assess the quality of the literature and overarch all types of study. For the purpose of this review, CASP was chosen as it identifies methodological flaws and considers its relevance to the outcome of practice.

Search terms used included generic and brand names for Melanotan I and II including "Melanotan I", "Melanotan II", "afamelanotide", and "tanning peptides" in combination with additional search terms including "desired effects", "side effects" "adverse effects", "adverse reactions" and "harms". These search terms were generated from analysis of the key concepts of the research topic – clinical outcomes of melanotan use. Publications from 1960 to the present day were included in the literature search, as this covers the period during which afamelanotide was being developed and subsequently marketed. Original empirical research was collected using electronic databases relative to health science including Psyinfo, Pubmed, Science Direct and Wiley Online with additional references suitable for inclusion in the literature review found in the reference lists of published works ($n = 7$).

Through database searching, 2253 records were identified and 767 records remained after duplicates were removed. Remaining