Microneedle Patch Use Among Those with Needle Phobia--Are All Needles the Same?

Editorial

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Introduction

A strong indication that the "writing is on the wall" for needle injection is evident in the stunning breadth of ingenuity being applied in the field of transdermal drug delivery technology (TDDT) to develop alternatives to needle injection. Transdermal patch products employing microneedle-mediated drug delivery technology (MDDT) have been widely touted as a solution for a number of well-recognized adverse events associated with needle injection such as pain and infection. MDDT may be considered the next evolutionary step in the miniaturization of drug delivery by needles at the micron scale (i.e. microneedles), intended to supplant the already shorter and smaller bore embodiments of the hypodermic needle that are barely visible to the naked eye. Elimination of pain from the user experience of needle-mediated drug delivery as a result of technologic advancements culminating in MDDT would represent a significant achievement. However, fear of pain associated with needle injection is not synonymous with fear of needle injection--commonly referred to as needle phobia. For individuals who are highly fearful of needles, avoidance of healthcare is common and may be presumed to cause significant morbidity and mortality.

Needle phobia is a medically defined condition in DSM-V and ICD-10. Fear and anxiety of "needle-injection-injury" may be induced by the perception of either a specific object (e.g. hypodermic needle) or situation (e.g. needle injection) associated with needle injection. A subgroup with severe needle phobia has an inherited susceptibility to vasovagal syncope. Taking vaccination as an application of MDDT in this Editorial, the key question with broader implications is no longer simply whether MDDT can eliminate pain associated with vaccination, but whether a microneedle vaccine patch (MVP) for vaccine delivery, as both an object and related clinical context, will reduce or eliminate fear, anxiety, vasovagal syncope, or avoidance behavior in persons with needle phobia.

The urgent and unmet need for a simple product such as a MVP that will enable self-administration among large global populations, begs the question whether a person with fear of needles can self-apply a MVP. Given the likely and imminent commercialization of MVPs, it would seem timely to address the impact of widespread adoption of microneedle patches and their use in global implementation of vaccination of children and adults. In this context, how we address needle phobia, which remains a highly prevalent (up to 40%) and neglected condition that is underdiagnosed in the healthcare setting, has therapeutic, social, and ethical implications.

History of Transdermal Delivery by Needle Injection

We live in an unprecedented time in human history when the ever growing "cloud" of public information is available just a few clicks away on our ubiquitous PDAs. The latest research discoveries, advancements, and websites/blogs are readily searchable, including those related to vaccines and vaccination or needle phobia. Since I am invoking history, what follows is a brief time line from what we refer to as "inoculation"--to imply physical breach of skin to at least the dermis--to the current universal understanding of vaccination.

The practice of inoculation may have originated in India in 1000 BCE, even as it is evident in the works of Homer (1102 BCE). Old Testament writings also refer to inoculation, placing the time before the 3rd century BCE. It was widely practiced during the reign of the Longqing Emperor (1567-1572) during the Ming dynasty (1368-1644), just as it was in pre-17th century Rome.

In the modern era, vaccination by inoculation was already widespread in England and America for at least half a century before Jenner developed the smallpox vaccine of 1793. Wren is the first to be confirmed to have used crude needles to do hypodermic injections on dogs. Dr. Francis Rynd is generally credited with the first successful injection in 1844, while Dr. Alexander Wood introduced the all-glass syringe for needle injection in 1851, which was patented in short order in Scotland in 1853.

Notably, Dr. Charles Hunter is credited with the coining of the term "hypodermic" in reference to subcutaneous (SQ) injection in 1858. Insulin was "discovered" and purified by Banting and Best, first delivered as subcutaneous injections to persons with type 1 diabetes, and promptly commercialized in 1922; it was a busy year. My reference for all of the above is Wikipedia--my go-to source for richly annotated and well cited information accessible within 60 seconds.

So, here we are in 2016, which marks the 223rd year since Jenner's history-making contribution to the field, the 163rd year since the all-glass syringe used in conjunction with a needle was patented, and the 94th year since SQ injection was used to deliver insulin to children with type 1 diabetes mellitus.

Defining Needle Phobia

There is general agreement that needle phobia can be classified into three types [1]:

a. Vasovagal reflex reaction associated with syncope (i.e. fainting), presyncope (i.e. near-fainting), or rarely seizure (i.e. convulsions).

b. Classic phobia resulting from an early traumatic experience during a medical procedure involving a needle (e.g. blood drawing, IM vaccination, catheter insertion without local anesthesia).

c. Hypersensitivity to the pain caused by needle penetration. This type is present in less than 1% of the general population.

The vasovagal reflex form of needle phobia is a defined medical condition. The American Psychiatric Association first formally recognized it in 1994 in its Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as a psychiatric medical disorder referred to as a specific fear of blood-injection-injury. It continues to be recognized to this day in DSM-V (2013) under the subcategory of Specific Phobias (Code 300.29) [2]. The corresponding ICD-10 code used in the US for reimbursement claim purposes has a specific diagnosis code for "Fear of Injections" (Code F40.231), which falls under the category of a specific (isolated) phobia [3]. Importantly, fear and anxiety is induced by either a specific object (e.g. hypodermic needle and syringe) or situation (e.g. injection). The specific object may be perceived as such in the most unlikely manner. In one reported case, a 16-year old healthy boy with needle phobia experienced vasovagal syncope while putting on a contact lens: "When he put his finger and the lens close to his eye to insert a soft contact lens, he felt sick and dizzy and fell unconscious [4]."

The DSM-V diagnostic criteria for a specific phobia are summarized as follows:

"Individuals with specific phobia are fearful or anxious about or avoidant of circumscribed objects or situations. [...] The fear, anxiety, or avoidance is almost always immediately induced by the phobic situation, to a degree that is persistent and out of proportion to the actual risk posed [2]."

The earliest usage of the phrase "needle phobia" appears in the title of a long overlooked case report in 1976 of the management of severe needle phobia in the situational context of blood drawing and intravenous catheter insertion [5]. The most frequently cited publication on needle phobia as a neglected diagnosis is by Hamilton, entitled "Needle phobia: a neglected diagnosis" [6]. Notably, this landmark paper was published in 1995, only a year after needle phobia was first defined in DSM-IV. Yet it remains the authoritative reference cited by scant peer-reviewed publications and on-line resources [1,7] devoted to this topic that have followed. Not surprisingly, what literature exists comes from the medical, pediatric, dental, and surgical settings in which needle injection, blood drawing, or catheter insertion (with a needle trocar) are routine. Notably, the medical literature is found specifically in family medicine or pediatric journals, as in the case of Hamilton's 1995 article [6], suggesting that current awareness of this condition, however inadequate, lies primarily among primary care providers.

Hamilton is referred to as an expert in the field despite this singular contribution. Actually, he published an earlier case report in 1991, largely ignored in the shadow of his 1995 paper [6], describing his own experience of apparent vasovagal syncope during which his blood pressure dropped from 130/90 to 70/0 mmHg after needle insertion [8]. It would appear that his interest in needle phobia was quite personal, but not a career pursuit. Hamilton and others emphasize several key features of the vasovagal form of needle phobia that distinguish it from the more common traumatic early experience with needles such as painful blood drawing, IM vaccination, or even blood transfusion [6-10]:

a. Affected individuals cannot typically identify the origin of needle phobia.

b. A familial form exists in which genetic susceptibility to a physiologic "vasovagal shock reflex" [6] triggered by needle puncture.

c. In the inherited form, there is an underlying autonomic dysregulation predisposing to neurally mediated syncope that can be evoked even in the absence of any blood-injection-injury stimulus [10].

d. This neural dysfunction may secondarily lead to needle phobia from successive needle exposure associated with repeated syncopal events [6,10].

e. Pharmacologic and non-pharmacologic interventions have proven to be effective in prevention and management of children and adults with needle phobia (see last section).

f. Clinical intervention is underutilized because needle phobia remains a neglected condition that is underdiagnosed, underreported, and underappreciated by healthcare workers who are largely unaware of its existence as a medical condition, and/or are not educated in its recognition or management.

Epidemiology of Needle Phobia: Prevalence, Morbidity, and Mortality

Hamilton estimated that the prevalence of needle phobia of the vasovagal was as high as 10% of the general population in 1995 [6]. Since persons with needle phobia typically avoid medical care, the prevalence is difficult to determine. Since 1995, needle fear has risen from 10% to 25% of adults and two-thirds of children [11]. Baxter suggests that at least one possible cause of this dramatic increase is that starting in 2000 (at least in the US), children began receiving 30 IM vaccine injections before age 6 [12]. She cites data from her unpublished study demonstrating that in children between age 4-6 years old (i.e. "old enough to remember"), the more injections they received on one day, the significantly greater chance they would be afraid of needles 5 years later.

Determining true prevalence is problematic due to the different criteria used to define needle phobia, which may result in either under or overreporting. Recent studies in the setting of a general adult medical practice in Queensland, Australia [13] and a travel clinic in Haifa, Israel [14] suggest an overall prevalence of 22% and 21.7 %, respectively. 20.5% in the Queensland study reported a level of fear of needles sufficient to cause avoidance of medical care in certain circumstances, while 8.2% in the Haifa study described

their fear as "unreasonably intense." Multivariate analysis revealed that a history of fainting was highly and independently associated with injection phobia, suggesting that the Haifa study design and analysis more accurately identified those with the vasovagal form of needle phobia. Recently, Cemeroglu et al. [15] distinguished between the prevalence of three types of needle phobia among children with type 1 diabetes mellitus (T1DM) on multiple daily injections or continuous insulin infusion: "fear of self-testing" (i.e. finger stick blood glucose monitoring; 10%), and "fear of injections" or "fear of infusion-site changes" (32%) [15]. Clearly, we can conclude that needle phobia--however it is defined or described--is highly prevalent.

Avoidance or refusal of medical care by those persons with needle phobia translates directly (e.g. urgent need for therapeutic injection) or indirectly (e.g. non-urgent need for vaccination) to increased morbidity. In the Queensland study, one-third and two-third of the "fear of needles group" anticipated avoidance of future vaccination with tetanus and flu vaccine, respectively, while one out of four adults anticipated avoidance of future injections of analgesia for pain control [13]. Cemeroglu et al. [15] also reported that children with T1DM with a more intense fear of needles performed less blood glucose monitoring and were more likely to have inadequate glycemic control [15]. However, this is only half of the equation. Identification of those children with needle phobia who have vasovagal symptoms such as dry mouth, feeling sweaty, shortness of breath, nausea, and faintness/dizziness associated with needle injection may allow for early and proactive interventions to alleviate the vasovagal reflex response and to improve glycemic control. Increased awareness, diagnosis, and education in the management of needle phobia by healthcare providers are critical to any effort to reduce avoidance of medical care and its negative consequences.

Is needle phobia a potentially fatal condition? There have been no studies to suggest the frequency of needle phobia as a cause of death. Hamilton reported 23 deaths due to needle phobia in a group with the severe vasovagal form, one of whom was his father [6]. The precipitous drop in blood pressure and imminent shock during a syncopal/pre-syncopal event may precipitate cardiac arrhythmia or acute coronary syndrome.

Microneedle Vaccine Patches and Needle Phobia

An estimated 12 billion injections for medical care and 100 million childhood vaccinations are given annually worldwide [16]. This is reason enough--aside from the fact that this is an editorial in an international journal devoted to advancements related to vaccines and vaccination--to use MVP commercialization, adoption, and global implementation as an example of MDDT products for which the numerous healthcare setting(s) in which they will be administered has important implications for persons with needle phobia.

By clinical definition of needle phobia in DSM-V, whether a MVP for vaccine delivery will reduce or eliminate the induction of a needle phobic response or allow for self-administration, would appear to depend on whether a MVP is *perceived* as a specific object intended for needle injection or in the context of vaccination. In other words, will a MVP be thought of as an object that can cause needle-injection-injury in the same way as a conventional hypodermic needle? Or even more concisely, is it the case that "a (micro) needle is a needle is a (micro) needle?"

To answer this question, we need to describe a microneedle vaccine patch in generic physical terms [17]. Microneedles are sub-millimeter structures designed to pierce the stratum corneum (i.e. outermost armor-like plating of skin and rate-limiting barrier to transdermal drug delivery) and deliver vaccines or drugs into the epidermis or dermis compartments of full-thickness skin. Regardless of design (e.g. solid, coated, dissolving, hollow), patches are typically arrayed with hundreds of microneedles manufactured to a height of only a few hundred microns from a base substrate. These microneedle arrays most commonly have a "pin cushion" appearance with sharp, pointed, needle-like tips designed to pierce the stratum corneum and deliver payloads of antigen to the underlying skin layers rich in Langerhans cells and dermal dendritic cells to elicit immunogenicity. Microneedles are by appearance and purpose identical to conventional hypodermic needles used for vaccination. The difference is that microneedles are invisible to the naked eye. A MVP at the macroscopic level has no visually detectable component that even remotely resembles a needle. They resemble, for all extensive purposes, a conventional band-aid or drug patch.

Why not just Avoid Mentioning "Needles/Microneedles/Cannulas" When Offering and Administering Invasive Patch Products?

Case report

My 6-year old son, like all children with access to standard pediatric care in the US, has now received all 30 of his intramuscular vaccine injections. His needle phobia was expressed only in relation to three occasions between the ages of 3-5 when he required local injection of lidocaine for anesthesia prior to receiving stitches. On the last occasion, four adults could not hold him down as he tried to get off the exam table, kicked, and screamed, "No needle!" He required sedation with intranasal versed before suturing of a traumatic wound could be safely performed. He is now nearly 7-years old. When I asked him a moment ago if a microneedle patch, comprising multiple rows of tiny microscopic needles that are so small they cannot be seen or cause pain or bleeding would allay his fear or anxiety as an alternative to needle injection of lidocaine (he remembers that last suturing episode, versed notwithstanding), he asked me how to spell "microneedles" as he typed the search word on Google. Soon, he was viewing images of microneedles on his iPad. His expert assessment: "I think it is even worse because the tinier the needle, the sharper the point." He was viewing an image of something that looked like a bed of pin cushions, the surface of a hand held meat tenderizer, or a so-called pin frog used for sticking on stems for flower arrangements. In the Japanese zen practice of ikebana, flower stems are pushed onto the pins of a kenzan, which is literally translated as "sword mountain."

There are increasingly frequent and disturbing claims of "needleless" or "needle-free" technology plainly advertised on the home pages of numerous pharma/biotech companies developing therapeutic MDDT products. Euphemisms such as "protrusions" or "extensions" *in lieu* of "microneedle" are not uncommon. A

recent press release for a new flat hardware device called an "insulin patch" did not once mention how the insulin contained in the reservoir is delivered across the skin. Is it through MDDT or cannula or a similar method that requires puncture of the skin? It's not clear because it is not addressed. What is clear is that it is not by passive transdermal delivery like an estrogen patch.

Is there a scientific basis for clinical guidelines to address needle phobia in general? There are numerous interventions that have been reported to have at least some effectiveness, especially in combination, such as distraction with cartoons, hypnosis, virtual reality, parent positioning and injection technique, needle desensitization techniques, or early positive learning experiences for reducing pre-procedural distress, anxiety, and the perception of pain. Indeed, there are published guidelines, randomized trials, and meta-analyses [18-20]. As discussed above, early or first experiences in the context of needle injection play a highly significant role in shaping later responses in adulthood. Further research remains to be done in this relatively new field to identify the most effective approaches alone or in combination.

How about studies of interventions for microneedle patches in particular? Mooney et al. [21] published a report of 86 children (aged 101-14) in 13 "focus groups" throughout Northern Ireland. Among other opinions the participants expressed, the following sentences stand out:

"A [microneedle] patch-based design enabled minimal patient awareness of the monitoring procedure, with personalized designs, e.g. cartoon themes, favored. Children's concerns included possible allergy and potential inaccuracies with this novel approach; however, many had confidence in the judgement of healthcare professionals if deeming this technique appropriate. They considered pediatric patient education critical for acceptance of this new approach and called for an alternative name, without any reference to 'needles'."

Notably, the authors published a paper on the potential for hydrogel-forming and dissolving microneedles for use in children the following year [22]. This is advance marketing at its best--or worst.

Without debating the validity of the methodology used to draw conclusions from their focus group of child participants, invoking an opinion "calling" for an alternative name for a microneedle patch without reference to "needles" by authors who are actively involved in scientific studies of the feasibility of microneedle patch technology--this is a grave disservice to the pharmaceutical and biomedical device industry whose efforts are intended to advance the health and well-being of these very children. Such efforts are guided by an ethical principle embodied in the Hippocratic Oath, "First do no harm." I will leave it to the reader to decide whether not making "[…] any reference to 'needles'" is acceptable on any level and whether it is a violation of this sacred oath. Should we also not mention the reason why the administration site needs to be cleaned with an alcohol wipe? How will we explain the cause of "microneedle-associated cellulitis" when it occurs, which it will even if in a minority of cases?

If not with reference to "needle," what alternative name for a microneedle patch would anyone like to suggest?

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Conflict of Interest

S.I. Hsu is the CEO/CSO of Prometheon Pharma, LLC.

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