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Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions

GERHARD BAUER,[a] MAGDI ELSALLAB,[b] MOHAMED ABOU-EL-ENEIN[b]

Key Words. Stem cells • Mesenchymal stromal cells • Stem cell tourism • Stem cell clinics • Unproven interventions • Regulations • Clinical trials • Ethics • Adverse events • Risks • Hype

[a]University of California Davis, Institute For Regenerative Cures (IRC), Sacramento, California, USA; [b]Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité – Universitatsmedizin Berlin, 13353, Berlin, Germany

Correspondence: Mohamed Abou-El-Enein, Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité – Universitatsmedizin Berlin, 13353 Berlin, Germany; e-mail: mohamed.abou-el-enein@charite.de

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ABSTRACT

The promise of stem cell (SC) therapies to restore functions of damaged tissues and organs brings enormous hope to patients, their families, loved ones, and caregivers. However, limits may exist for which indications SC therapies might be useful, efficacious, and safe. Applications of innovative therapies within regulatory boundaries and within the framework of controlled clinical trials are the norm in the scientific and medical community; such a system minimizes patient risk by setting a clear and acceptable safety and efficacy profile for new therapeutics before marketing authorization. This careful clinical validation approach often takes time, which patients suffering from terminal or debilitating diseases do not have. Not validated, unproven stem cell interventions (SCI) that promise a working treatment or cure for severe diseases have therefore found their way into the patient community, and providers of such treatments often take advantage of the public's willingness to pay large amounts of money for the misguided hope of a reliable recovery from their illnesses. We conducted a review of scientific publications, clinical case reports, and mass media publications to assess the reported cases and safety incidents associated with unproven SCI. The review also analyzes the main factors that were identified as contributing to the emergence and global rise of the "stem cell tourism" phenomenon.
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SIGNIFICANCE STATEMENT

Recent reports have been documenting the increase in clinics advertising unproven stem cell (SC) interventions which promise to treat and even cure certain diseases, despite the lack of scientific evidence for their safety and efficacy. This review presents a detailed, up-to-date assessment of the available, reported cases receiving such interventions. This assessment is highly significant, as it joins other efforts in shedding new light on the magnitude and pervasiveness of a critical situation which may pose a serious risk to vulnerable patient populations and, at the same time, may dilute the value of ethical and legitimate SC therapies currently being developed for patients through rigorous preclinical and clinical testing.

The unique ability of stem cells (SCs) to self-renew has prompted basic and clinical investigators to explore their utility for functional restoration of damaged or diseased tissues and organs [1–3]. Results obtained from investigations of different SC types have demonstrated great potential for treating various previously untreatable medical conditions [2, 4, 5]. However, SC research is also often associated with inflated expectations over regenerative capabilities, and the ability to bring working therapies to diseases currently listed as "unmet medical needs" [6, 7]. Although such notions have created significant support for funding legitimate SC research, they have also created strong public demand for the immediate availability of novel SC treatments. This gap between the potential of medical innovation and unmet medical needs has created an opportunity for many dubious "stem cell clinics" to promise availability of SC therapies for various conditions, while providing neither proper scientific support nor validated clinical experiences for these claims. Several publications have attempted to quantify the magnitude of this problem by collecting online information on clinics and businesses in different countries offering unproven stem cell interventions (SCI)

for both cosmetic and medical purposes [8–19]. These thinly disguised for-profit businesses continue to exploit a wide base of vulnerable patients, using unproven therapeutic claims that solicit false hopes of providing new and effective treatments. As unproven SCIs do not have the benefit of payor/insurance coverage, patients are also exploited financially by being charged thousands of dollars to receive these unproven interventions. According to Srivastava et al., unproven cellular therapies are characterized by an unclear scientific rationale, an unknown mechanism of action, insufficient preclinical data regarding their safety profile, unconfirmed product quality, inadequate information disclosure to the patient, untested administration methods, and uncontrolled experimentation in humans [20].

Several guidelines and recommendations have been proposed to limit or eliminate such practices [7, 21–28], and patient advocacy groups and medical societies have been encouraged to work together, in conjunction with regulatory agencies, to raise awareness and educate physicians and patients about the differences between properly tested SC therapies and unproven SCIs [29, 30]. Despite these efforts, unregulated access to unproven SCIs seems to continue to progress, with current regulatory and legal actions unable to control it. In this review, we offer a comprehensive retrospective analysis of adverse events reported for patients receiving unproven SCIs, while capturing factors that contribute to their on-going use.

Stem Cells: Separating Hope from Hype

The continuing SC plethora and the associated ethical controversies started at the end of the 20th century with the isolation of pluripotent SCs from the inner cell mass of early human embryos by James Thomson (University of Wisconsin, U.S.) and from fetal gonadal cells by John Gearhart (Johns Hopkins University, U.S.) [31, 32]. Soon after, the ability to differentiate pluripotent SCs ex vivo into specialized tissue cells of ectodermal, mesodermal, and endodermal lineages was demonstrated [33]. In 2006, Shinya Yamanaka (Japan) generated induced pluripotent stem cells (iPSCs) from differentiated, mature cells normally incapable of reverting back into true SCs, by up-regulating early acting transcription factors using inserted genes [34]. Nevertheless, the ethical controversies resulting from human embryo sourcing for the generation of embryonic stem cells (ESCs) have hindered the wide spread clinical use of ESC derived products. Likewise, translational challenges and adverse events experienced in clinical trials of iPSC derived cellular products have limited their clinical applications [35–37].

Adult-type SCs are presently a much more feasible and immediate option for clinical applications, with less ethical controversy [38]. Mesenchymal stromal cells (MSCs), which function as multipotent adult SCs, have intrigued the scientific community with their potential therapeutic effects, resulting in many clinical trials but few marketing approvals [39, 40]. Adipose tissue-derived MSCs have become the most popular cell type exploited by many spurious SC clinics because of cell harvesting ease through relatively minor procedures, such as liposuction [9, 41].

Researchers' over-enthusiasm and media portrayal of scientific achievements in regenerative medicine by applying adult-type SCs has overly inflated the potential of such therapies suggesting wide availability of diverse SC-based treatments in the near future [42]. This coverage fuels public expectations for accelerated access to such treatments and creates opportunities for deceptive trade practices without evidence [43, 44]. To eventually generate a safe and efficacious product, the clinical development path for SC and other somatic cell and gene-based therapeutics is long and financially draining [45]. Therapeutic SC reality, therefore, falls far short of these expectations, and unproven SCI offerings abound unregulated to fill this gap.

Safety Incidents Reported After Receiving Unproven SCs

To evaluate the potential risks of receiving unproven SCIs, literature, and web-based searches were conducted for available adverse event cases reported to date (see Tables 1–2). PubMed and Google search engines were used during January, 2018 to locate cases describing acute or chronic complications as well as death after administration of unproven SCIs into humans. The following terms and keywords were used interchangeably during the PubMed search: "unproven," "unauthorized," "Stem cell," "interventions," "tourism" and "clinic," and in addition the following terms were added during the Google search: "complication," "death," "neoplasm," "tumor," "infection," and "inflammation." Searches were limited to English-language literature, with no date limits. Scientific literature and also mass media reports were reviewed by two independent reviewers for inclusion of relevant evidence. Differences in selections were addressed by discussions producing mutual agreements. Additional cases were identified through supplemental materials (e.g., review articles) not identified in the initial search.

The PubMed database search yielded 885 results that were reviewed together with the first five pages of the Google search results. A total of 35 cases describing acute or chronic complications or death following an alleged SCI administration were identified: 19 cases came from the scientific literature, and 16 cases were mass media reports (Tables 1–2). To assess the reliability of the reported cases, reporting criteria for identified cases in the scientific literature were evaluated against the CARE case report guidelines [69]. Reports failing to meet these reporting criteria were categorized as inadequate (n = 9). Although they were meant to be written in the most understandable lay language, some media reports of patients receiving unproven SCIs showed high level of technical details in reporting (n = 5), enabling us to extract all necessary information. This level of responsible reporting is encouraged and considered a powerful tool for educating the public and the scientific community.

The first unproven SCI adverse event from this search dates to 2001: a child (age 13 at the time of admission) suffering from ataxia telangiectasia, for which his parents took him to Russia in 2001, 2002, and 2004 to receive allogeneic fetal neural SC injections into both the cerebellum and the cerebrospinal fluid. In 2005, the child presented to Sheba Medical Center, Israel, complaining of recurrent headaches. An infratentorial brain lesion was identified by MRI, and the patient underwent brain surgery in 2006 to remove the lesion. Neuropathological examination of the mass confirmed a glioneural neoplasm originating from donor neural SCs [46]. In further cases examinations, 12 of 35 patients received adipose tissue-derived cells and three patients received xenogeneic SCs, none

Table 1. Reported cases in scientific literature which received unproven stem cell interventions

Gender	Age at diagnosis or death	Country of residence	Country where intervention took place	Condition	Alleged type of cellular intervention	Site of injections	Complications	Diagnosis	
Male	13 years	Israel	Russia (a clinic in Moscow)	Ataxia telangiectasia	Fetal neural stem cells (SCs)	Direct injection into the cerebellum and the cerebrospinal fluid (CSF)	Neoplastic	Glioneural neoplasms in the brain and the cauda equina originated from the donor neural cells	[46]
Female	46 years	Thailand	Thailand (private clinic)	Lupus nephrites	Hematopoietic SCs	Percutaneous injection into the renal regions on both sides (blindly)	Neoplastic	Multiple angiomyeloproliferative renal lesions	[47]
Female	17 years	United states	Costa Rica	Multiple sclerosis	Allogeneic cord blood mesenchymal stromal cells (MSCs) and autologous adipose derived stromal cells	Intrathecal injection and intravenous infusion	Neurological	Severe demyelinating encephalomyelitis	[48]
Male	66 years	United States	For profit clinics in China, Argentina, Mexico	Ischemic stroke	MSCs, embryonic, and fetal neural SCs	Intrathecal injections	Neoplastic	Glioproliferative lesions in the thoracic spinal cord and thecal sac, originating from exogenous cells	[49]
Female	63 years	United States	United States	Face lift	Fatty aspirate from the abdominal wall in a procedure called "stem cell face lift"	Facial injection	Infectious	Necrotizing metachronous facial ulcerations	[50]
Female	18 years	United States	Portugal	T10–11 fracture dislocation and associated spinal cord injury	Olfactory mucosal cells	Intraspinal transplantation	Neoplastic	Intramedullary spinal mass consisting of olfactory epithelium and large amounts of mucous	[51]
Female	72 years	United States	United States (For-profit clinic Bioheart Inc., known now as U.S. Stem Cell Inc.)	Age-related macular degeneration (AMD)	Autologous adipose derived stromal cells	Intravitreal injections	Loss of vision	Vitreous hemorrhage and possible retinal detachment in both eyes. One year after the injection, retinal atrophy and complete loss of vision in both eyes	[52]
Female	78 years	United States	United States (For-profit clinic Bioheart Inc., known now as U.S. Stem Cell Inc.)	AMD	Autologous adipose derived stromal cells	Intravitreal injections	Loss of vision	Vitreous hemorrhages, diffuse intraretinal and preretinal hemorrhages and retinal detachment in the left eye. One year after injection, perception of hand movement in the right eye and 20/200 vision in the left eye	[52]

(Continues)

Table 1. *Continued*.

Gender	Age at diagnosis or death	Country of residence	Country where intervention took place	Condition	Alleged type of cellular intervention	Site of injections	Complications	Diagnosis	
Female	88 years	United States	United States (For-profit clinic Bioheart Inc., known now as U.S. Stem Cell Inc.)	AMD	Autologous adipose derived stromal cells	Intravitreal injections	Loss of vision	Retinal detachment with proliferative vitreoretinopathy in the right eye and geographic atrophy with a superotemporal cryopexy scar in the left eye. One year after the injection, visual acuity was perception of hand movement in the right eye and light perception in the left eye	[52]
NA	19 years	NA (Western country)	China	Spinal cord injury	Olfactory ensheathing fetal cells (OECs)	Spinal injection	Infectious	Meningitis, CSF pleocytosis	[53]
NA	22 years	NA (Western country)	China	Spinal cord injury	OECs	Spinal injection	Infectious, gastrointestinal	Meningitis, gastrointestinal bleeding, pneumonia.	[53]
NA	22 years	NA (Western Country)	China	Spinal cord injury	OECs	Spinal injection	Infectious	Meningitis, Stevens-Johnson syndrome	[53]
NA	35 years	NA (Western country)	China	Spinal cord injury	OECs	Spinal injection	Febrile illness	Fever, headache	[53]
NA	47 years	NA (Western country)	China	Spinal cord injury	OECs	Spinal injection	Febrile illness	Fever	[53]
Female	27 years	Egypt	Egypt	Acute transverse myelitis	MSCs	Intrathecal injection	Autoimmune reaction	Acute disseminated encephalomyelitis	[54]
Male	41 years	NA	NA	Hypertrophic cardiomyopathy	Autologous “precursor” cells	Myocardial injection	Cardiovascular	Ventricular fibrillation	[55]
Male	41 years	NA	NA	Cervical herniated intervertebral disc	Adipose derived MSCs	Intravenous infusion	Cardiovascular	Pulmonary embolism	[56]
NA	NA	UK	Netherlands	NA	Stem cells (not specified)	NA	Autoimmune reaction (allergic)	NA	[57]
Female	71 years	NA	Japan	Chronic kidney failure	Adipose derived MSCs	Intravenous infusion	Neurological	NA	[58]

Table 2. Reported cases in mass media which received unproven stem cell interventions

Gender	Age at diagnosis or death	Country of residence	Country where intervention took place	Condition	Alleged type of cellular intervention	Site of injections	Complications	Diagnosis	
Male	18 months	Italy	Germany (Xcell Center)	Not specified neurological condition	Bone marrow derived stem cells (SCs)	Direct injection into the brain	Neurological	Internal brain hemorrhage, death	[59]
Male	10 years	Azerbaijan	Germany (Xcell Center)	Cerebral palsy	Bone marrow derived SCs	Direct injection into the brain	Neurological	Internal brain hemorrhage	[59]
Female	69 years	United states	Dominican Republic (For-profit procedure performed by Dr. Zannos Grekos)	Leg numbness and difficulty walking after breast cancer chemotherapy related complications	Grossly filtered bone marrow aspirate	Injection into the right carotid artery	Cerebrovascular	Stroke, death	[60]
Male	77 years	United States	Dominican Republic (For-profit procedure, supervised by Dr. Zannos Grekos)	Pulmonary hypertension	Adipose derived stromal cells	Intravenous infusion	Cardiovascular	Cardiac arrest, death	[60]
Male	73 years	South Korea	Japan (RNL Bio)	NA	Adipose derived stromal cells	NA	Cardiovascular	Pulmonary embolism, death	[61]
Male	61 years	South Korea	China (RNL Bio)	Diabetes	Adipose derived stromal cells	NA	NA	Death	[61]
Female	59 years	United states	United States (Bioregenesis Institute)	Idiopathic bronchiectasis	Non-specified stem cell intervention	NA	NA	Death	[62]
Male	27 years	China	China (Chinese army's 455 PLA Hospital)	Disabilities from a minor stroke	Allogenic SCs (not specified)	Spinal and intramuscular injections	NA	Death	[63]
Female	63 years	China	China (Beijing Military General Hospital)	Hepatitis B related lifelong liver cirrhosis	NA	NA	NA	Coma, death	[63]
Female	NA	United states	United States (a clinic in Beverly Hills)	Face lift	Adipose derived stromal cells	Injections around the eye	NA	Bone-like growth in the eye lid	[64]
Male	72 years	Philippines	Germany	Liver cancer	Animal based (xenogeneic) SCs	NA	Infectious	Pneumonia	[65]
Male	77 years	Philippines	Germany	Pneumonia	Animal based (xenogeneic) SCs	NA	Infectious	Pneumonia	[65]
Male	NA	Philippines	Germany	Heart disease	Animal based (xenogeneic) SCs	NA	NA	NA	[65]
Female	75 years	Australia	Australia (Macquarie Stem Cell Clinic in Liverpool)	Dementia	Autologous adipose stromal cells	NA	Cardiovascular	Uncontrolled blood loss during the liposuction procedure, hypovolemic shock, and death	[66]
Female	NA	Australia	Russia (the National Pirogov Medical Surgical Centre)	Neurological disorder, stiff person syndrome	Autologous hematopoietic SCs	Intravenous infusion	Cardiovascular	Heart attack, death	[67]
Male	58 years	Russia	Russia	Aging	Human embryonic SCs	Skin injection	Neoplastic	Pea sized tumors	[68]

of which had regulatory approvals or clinical trial designations. Clinics involved in offering such unproven SCIs to patients who subsequently suffered adverse events or died were located in 14 countries. Some patients had located those clinics through the internet. In one incident, three patients identified the intervention through "Clinicaltrials.gov," where a company, Bioheart, registered a trial (NCT02024269) for intravitreal injection of adipose-derived SCs to treat age-related macular degeneration (AMD). The trial was withdrawn before patient enrollment began. A later publication, however, revealed that the three patients suffered severe vision loss after the administration of the aforementioned unapproved "Bioheart" product [52]. The patients were also persuaded to pay $5,000 each to participate in the alleged study [52].

Cell preparation protocols for clinical applications could only be identified in four cases [46, 51, 52, 70]. In one case, filtered bone marrow was applied and described as "grossly filtered" before being injected directly into the carotid artery [60]. In another case, harvested abdominal wall fat was mixed with several hormones and injected into the face in what was called a "stem cell facelift" [50]. One patient traveled to clinics in China, Mexico, and Argentina to receive SCIs and ended up with a glioproliferative lesion originating from cells implanted in the thoracic region of the spinal cord [49]. A review of these results, consistent with previous analyses [8], indicates that administration of SCIs not subjected to proper testing, accepted manufacturing standards and clinical supervision can, at least in some cases, pose serious risks. While some of the injured patients sought legal action against providers offering unproven SCIs, most lawsuits have reached a settlement with no judicial decisions against these practices [71].

Factors Contributing to the Emergence and Global Rise of Unproven SCI

Based on the cases collected, we identified three domains that may contribute to on-going use of unproven SCIs with strong relationships between each other: the ethical domain, constituting the main concern, where promises of SC therapies to the public should be truthful and accurate, the scientific domain, where safety and efficacy of the treatment should remain a foremost priority, and the regulatory domain, where a balance should be struck between accelerated SC-based therapeutic development and compiling well-characterized benefit-risk profiles based on available safety and efficacy data to ultimately benefit patients.

The Interface Between Ethics and Rigorous Scientific and Clinical Research

Despite some studies describing MSC risks of promoting tumor growth and certain infections [72], MSCs are considered safe when tested in carefully designed, well-controlled clinical studies and applied in indications suited to their applications [73]. Preclinical testing including in vitro and in vivo assays based on well-designed experiments are essential to ensure sufficient knowledge of the safety and efficacy of a treatment before administration into humans [74]. All new cellular therapy products tested clinically should be produced under Good Manufacturing Practice conditions and tested under Good Clinical Practice to ensure consistent quality of the administered product, the clinical competence of personnel administering the therapy, and the safety and well-being of clinical trial participants [74, 75]. This rigorous code of conduct is meticulously adhered to by all approved, legitimate clinical trials investigating SC-based therapies to ensure adequate evidence synthesis [76, 77]. This process is also subject to thorough quality systems, in which documentation and reporting play a major role [78]. In contrast, SC clinics and companies treating patients in inadequately equipped facilities with nonqualified personnel do not adhere to these criteria. These clinics usually fail to establish requisite safety and efficacy profiles for their SCIs as mandated by regulations, and thus lack the knowledge and accountability for proper dose regimens, SC quality and counts, and optimal route and method of administration [41]. Moreover, objective treatment information for cases of unproven SCIs is generally lacking, relying primarily on patient testimony. This makes traceability challenging and cannot ensure that data and reported results are credible and accurate, and moreover, it cannot guarantee that patient rights, integrity, and confidentiality were protected. This *modus operandi* places treated patients at great risk, leading to serious adverse events, directly or indirectly related to SCIs. Lack of proper safety reporting also extends to human studies investigating novel therapies [79].

Aside from questionable scientific rigor for using unproven interventions, the dilemmas surrounding these practices challenge the ethical boundaries of honesty and dignity, with direct impact on genuine rights of human autonomy—a primary motive for swift actions and de facto solutions [80]. In most of the reported cases, patients were desperate with noncurable chronic disease where the "right to try" concept to administer experimental treatments operates [44]. This desperation adds complexity to treatment scenarios since clinics offering unproven SCIs also develop strategies to exploit these desperate patients [42, 80]. Not all SC clinics take the same approach, but many websites advertising such interventions repeat a general theme featuring sentimental messaging and patients' testimonies to benefits and cures. Patients seeking these services have been found to use crowdfunding campaigns with captivating personal narratives and misleading statements about potential benefits and absence of risks to defray the costs of the procedure [81]. The question raised is often: "Is it ethical to administer an unproven intervention that might provide a benefit, but has not been subjected to accepted standards of scientific and clinical research rigor and evidence?" The rise of the "right to try" argument compels heavy refocus on the scientific and ethical bases behind current medicinal product testing and approval frameworks. Despite possibilities for vast improvements that might be introduced into such frameworks, current regulatory pathways remain the best guarantee for both quality and safety of newly approved products to protect patients from potential harm. Most importantly, physicians who are involved in offering or providing unproven SCIs which lack the appropriate scientific evidence, are violating the trust of their patients and subjecting them to unjustifiable risks [82].

Regulatory Issues Related to the Use of Unproven SCI

Currently, the U.S. has the largest number of SC clinics globally [10]. In 1997, the Food and Drug Administration (FDA) established a regulatory plan for human cells, tissues, and cellular or tissue-based products (HCT/Ps). This was followed by three separate parts and rules in 1998, 1999, and 2000, to be implemented together in Title 21 of the Code of Federal Regulations Part 1271 (21 CFR 1271) in 2001 [83], becoming active in May, 2005.

According to 21 CFR 1271, HCT/Ps are not considered biological products and not regulated by the FDA when they are minimally manipulated, intended for homologous use, or if they are removed and implanted into the same patient in the same surgical procedure. This description has shown to be key to enabling unproven SCIs. Many unproven SC clinics escape FDA regulatory scrutiny by claiming that their therapy falls under these criteria and therefore does not require FDA approval. To clarify this situation, the FDA published two guidances in 2014 [84, 85] stating that the techniques used during the preparation of SC-based therapies isolating the stromal vascular fraction are not considered "minimal manipulation." The FDA also clarified their criteria for the "same surgical procedure exception," and that such products are to be regulated as drugs, devices, and/or biological products (21 CFR 1271.20) and subject to Section 351 of the Public Health Service Act and applicable regulations [84]. Since 2011, the FDA has sent several warning letters to many dubious clinics that violate these rules [21] and has held several workshops to promote proper development of SC-based therapies [86]. Most FDA warning letters were for marketing an unproven SCI that falls under FDA authority. These letters also revealed that some companies that do not directly provide SCIs exploit the term "stem cells" in their marketing of devices and cosmetics for enhancing SC functions, or for activating or extracting SCs for reinjection. This pattern of exploiting scientific terms for device marketing, especially for cosmetics has also extended to other advanced therapeutics, such as gene therapies. Recently, the FDA published a warning statement about the "do it yourself" kits for gene therapy production and administration commercialized by a "biohacker" movement [87].

In the European Union (EU), SC-based therapies received official definition by the European Medicines Agency (EMA) in 2001 under Directive 2001/83/EC as "cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases" [88]. General aspects of cellular therapy were established in guidelines for human cell-based medicinal products (EMEA/CHMP/410869/2006). The 1394\2007 regulation established rules that regulate the Advanced Therapy Medicinal Products (ATMPs) throughout Europe under EMA authority. From 2008 to 2011, a transition period was allowed for all cellular therapy providers to comply with these new regulations [89]. The company XCell Center (Düsseldorf, Germany) exploited a legal loophole in the German regulations and the new EU regulations during this transitional period to provide bone marrow SC-based interventions. The Center closed in 2010 after the death of an 18-month old child from internal brain hemorrhage [90].

Several regulatory pathways are currently available to facilitate patient access to and benefit from therapeutics still being investigated under rigorous scientific research practices. This "compassionate use of investigational drugs" has a clear regulatory framework in both Europe and the U.S. Through the treating physician, patients in the U.S. who are terminally ill and fail to meet inclusion criteria for clinical trial enrollment can request access to investigational therapeutics. This access can be obtained through two pathways, either the "expanded access programs," where a drug or biologic in late stage development can be accessed by a wider patient base, or the "single patient expanded access" pathway, where the treating physician requests access to an unlicensed therapeutic from the manufacturer. The manufacturer decides to provide the patient with the experimental drug while simultaneous FDA approval for use is obtained [91]. Moreover, the FDA has implemented the Regenerative Medicine Advanced Therapy designation, offering incentives to developers of novel therapies, similar to the "breakthrough designation," such as accelerated approval, among others [92]. Although these legitimate tools are already available to enable accelerated access to potentially beneficial experimental therapies for severely ill patients, the current proposed federal "right to try" legislation in the U.S. may weaken the agency's enforcement ability [93].

In the EU, compassionate use allows member states to permit use of unlicensed medicinal products for patients with serious, debilitating, long lasting conditions. Another option is the hospital exemption, where use of ATMPs, including SC-based therapies, is possible for patients on an individualized basis and under the responsibility of the treating physician [94]. Accelerated development pathways for "unmet medical needs" products have also been developed in the U.S. and EU to encourage pharmaceutical companies to invest in such products and to accelerate product availability with shorter development timelines compared to regular therapeutics [94, 95]. Perhaps not coincidentally, "unmet medical needs" are the usual targets for unproven SCI providers. To that end, regulatory agencies are expected to implement a comprehensive policy framework and enforcement measures to clearly delineate SC therapeutic development that require agency oversight and to control the rising tide of direct-to-consumer marketing of unproven SCIs that put increasing numbers of patients at risk [22, 28].

Summary

Increasing use of unproven SCIs is a complicated, multifactorial problem that requires the attention of all stakeholders on national and international levels to be properly addressed. Collected evidence indicates substantial patient exploitation using the "power of hope," and risks using unproven SCIs. Two limitations to this review exist, making it challenging to draw strong correlations between unproven SCIs and reported safety incidents: first, the number of cases identified through a variety of search strategies is considered small and under-represented; second, most of the cases reported from both scientific publications and mass media suffer from incomplete information on the SCI applied. It is expected that the true number of cases receiving unproven SCIs is much larger than the one reported. This situation places more importance on proper adherence to international standards of ethics and science in designing, conducting, recording, and reporting clinical studies of new SC therapies, critical to protecting vulnerable patient populations and providing essential evidence for safety and efficacy determinations. Despite the recent action of the FDA to seek permanent injunctions against two SC clinics advertising unproven SCIs is being hailed as a triumph of law and science-based safeguarding over unethical and potentially dangerous practices [96], the current situation requires relentless and immediate responses to be sufficiently contained.

Author Contributions

G.B.: conception and design, manuscript writing; M.E.: conception and design, data collection and interpretation,

manuscript writing; M.A.: conception and design, data collection and interpretation, manuscript writing, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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