To: Drug Enforcement Administration

From: Anthony Roberts

Date: March 2023

Subject: DEA-407 Public Comment

COMMENT FOR DEA-407 NOTICE AND COMMENT PERIOD

EXECUTIVE SUMMARY

The newly proposed rule titled "DEA-407" modifies the RYAN HAIGHT ACT to allow the prescription of controlled non-narcotic drugs in Schedule III only after an in-person examination by the prescribing physician. Non-narcotic controlled substances in Schedule III include testosterone and all other anabolic androgenic steroids. These prescriptions are permissible under the proposed guidelines if a medical practitioner who performed the in-person examination refers the patient to the prescribing physician. Telehealth visits without a prior in-person medical examination by the prescribing medical practitioner or a referral from a medical practitioner who conducted a prior in-person medical evaluation have a 30-day initial prescription limit on non-narcotic controlled substances in Schedule III, with an in-person visit required for additional prescriptions. In addition, an in-person two-way audiovisual appointment would now be necessary for the examining physician to transfer the patient to the prescribing physician.

The Drug Enforcement Administration's published data and direct statements indicate that testosterone and other anabolic androgenic steroids do not meet the scientific criteria for inclusion under the Controlled Substance Act, and moreover that their diversion is not a significant risk (under 1%, but too minimal for a more accurate estimate); prescriptions for testosterone have been rising near-steadily since 2010, without a commensurate increase in diversion. In addition, since the current rules were adopted as part of the ongoing Public Health Emergency, a record number of patients have opted for telehealth, while the illegal sale of testosterone and anabolic steroids has decreased. This is despite, and potentially even resulting from, the flexibility afforded to telehealth practitioners. The newly proposed rules are demonstrably unnecessary as regards this class of medication.

The medical literature indicates a robust safety profile for testosterone and other anabolic steroids. Taken together, the empirical and scientific evidence weighs heavily against additional prescribing restrictions. These new, overly restrictive rules, undoubtedly impose an unwarranted burden on physicians, but also affect patient access to their medication—this is a broad cross-section of the population including veterans, transgender people, those with wasting diseases (such as HIV/AIDS and certain forms of cancer), hypogonadal men, the elderly, obese and diabetic people, and even women with hormone deficiency.

Broadly, DEA-407 may address a regulatory deficiency as regards other controlled non-narcotic drugs. But evidence that it should be applied to testosterone and other anabolic steroids is lacking or directly contradicted. Therefore, an exemption from the new rule is warranted. If this is not a

viable solution to the inapplicability of the rule and the medication class, the rule should be further tailored to reflect accepted medical practice. The two-way audio-visual handoff with the patient, the examining physician, and the prescribing physician all present is not practical or logical. Instead of the initial 30-day rule, a 90-day initial prescription is preferable, as this has greater support in literature and practice. Best practice indicates the need for a follow-up within 6-12 months, not within the first month. As the examining physician is not the prescribing physician, and the risk of diversion is below quantifiable levels, it is more reasonable to maintain the division of labor and the status quo for record keeping and licensing. Each doctor should only be required to maintain records of their direct involvement with the patient, and only for the prescribing physician to have the required DEA license.

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I. DEA-407 Procedural History

On 24 February 2023, the Drug Enforcement Agency ("DEA") announced amendments to the Ryan Haight Online Consumer Protection Act of 2008 ("Ryan Haight Act" or "RHA"). The amendments address, *inter alia*, the prescription of controlled non-narcotic substances via telehealth, and significantly alter 21 CFR 1300, 1304, and 1306. These regulations take effect on 11 March 2023 coinciding with the end of the ongoing Public Health Emergency ("PHE") waivers. Subsequently DEA published to the Federal Register under Docket No. DEA-407 on 1 March 2023, for the requisite notice and comment period.

In the corresponding docket entry, DEA proposed limiting the available options for telehealth. The first rule objected to herein is the new requirement that both the examining physician and prescribing physician are required to have a DEA license. The second rule objected to herein is that the prescribing physician must examine the patient within 30 days to continue dispensing non-controlled scheduled medicine after the allotted time. This is despite having been previously examined by a physician precedent to the prescribing physician dispensing the medication. In addition, it has been proposed that both doctors will be required to keep records that would previously have been held by either one or the other based on care provided. These changes create, without need, a far more restrictive prescribing environment than what has been in effect for the three years prior under the existent PHE waivers.

The new rules as set forth in DEA-407 that modify the RHA would allow the prescription of controlled non-narcotic medications in Schedule II, III, IV, and V, and the prescription of narcotic or Schedule II medication only after an in-person evaluation by the prescribing physician. When there is a referral under the proposed rules from a medical practitioner who conducted the in-person evaluation, these same prescriptions are allowed. However, under a telehealth visit without a prior in-person medical evaluation by the prescribing medical practitioner or without a referral from a medical practitioner who conducted a prior in-person medical evaluation, there is a 30-day initial prescription limit on non-narcotic controlled substances in Schedule III, IV, and IV, with an in-person visit required for additional prescription and no ability to prescribe Schedule II or narcotic medication.

The DEA's recently proposed amendments to amend RHA and modify 21 CFR parts 1300, 1304, and 1306 to authorize prescribing of controlled substances in specified limited circumstances are offered as consistent with effective controls against diversion and otherwise consistent with public health and safety. However, while there is undoubtedly an illegal market for anabolic steroids, diversion —the misdirection and misappropriation of legitimately manufactured domestic pharmaceuticals— has been effectively curtailed by the existing regulatory and legislative scheme.

Accordingly, this comment addresses the factual, medical, and legal rationale to warrant reconsideration of the aforementioned rules as well as the impact the rule will have on physicians' medical practices, the telehealth industry, and patients' access to hormone and testosterone replacement therapy (respectively "HRT" and "TRT"). [1]

[1] This comment will focus on testosterone but note that this hormone is currently not subject to any regulatory constraints or latitude beyond that of other anabolic androgenic steroids. Therefore, consideration given to testosterone should be applied to all hormones categorized as anabolic androgenic steroids.

II. Legislative and Scheduling History

Androgenic Anabolic Steroids (AAS) are Schedule III controlled substances under the Controlled Substance Act ("CSA"). They are also non-narcotic medications. They were not controlled under the original Act (1970), either specifically or categorically, but were subsequently controlled under a subsequent act in 1990, which added them as a definitional category to the CSA. Due to their unique status under the CSA, it is appropriate to treat them differently for the purposes of this proposed rulemaking; applying general rules not tailored to their unique medical use will result in unnecessary restraints being foisted on the telehealth hormone replacement therapy market. These restraints will greatly reduce their accessibility, utility, efficacy, and otherwise result in administrative burdens that could impede the existing standard of patient care.

This is unnecessary, as the pharmaceutical industry, through prior actions, have led the way with self-regulation and self-policing, well in advance of regulatory or legislative intervention.

For example, in 1983 Ciba Pharmaceuticals discontinued sale of the best-selling AAS on the pharmaceutical market (methandrostenolone, under the trademark "Dianabol"). Following this industry-set example, in December of 1985, the Food and Drug Administration (FDA) sent a letter to domestic pharmaceutical firms instructing them to discontinue sale of certain specified AAS, including generic forms of Dianabol. All notified firms complied with the FDA directive and AAS such as Dianabol were successfully removed from the domestic market. Neither legislative action nor the rulemaking process was required. However, as the direct consequence of this void in the U.S. market, a Mexican pharmaceutical firm increased production of the unavailable drugs and attempted to fill the void through smuggling AAS across USA/Mexico border[2].

Consequently, in 1988 the first bill attempting to regulate an anabolic steroid (specifically to add methandrostenolone to the CSA) was introduced to Congress. At the subsequent congressional hearing, the DEA testified in opposition to the bill.

> *"In this respect, the law is poorly suited to the steroid drugs. It is clear, based on the legislative history, that the Congress did not intend to encompass them within it."*[3]

On 29 November 1990, President George H.W. Bush signed the Anabolic Steroids Control Act (ASCA) of 1990. The act took effect on 27 February 1991[4]. The Act established and regulated AAS under Schedule III of the CSA by adding twenty-five known AAS to the list of controlled substances.[5] An act of the legislature was necessary to add anabolic steroids to the CSA because, as the DEA testified, they could not be added administratively. For a second time, DEA took the

[2] https://www.latimes.com/archives/la-xpm-1988-10-30-me-1039-story.html
[3] One Hundredth Congress, Second Session. Testimony regarding H.R. 3216. July 27, 1988.
[4] See generally: (Title XIX of Pub. L. 101-647), but see also DEA's explanation and promulgation of same at: https://www.regulations.gov/document?D=DEA-2011-0015-0001, at "Background Information."
[5] https://www.congress.gov/bill/101st-congress/house-bill/4658/text

official position that AAS failed to meet the criteria for scheduling, putting forth serious doubts as to the propriety of using the CSA to regulate this category of medicine.

> *"The Controlled Substances Act is built entirely and exclusively around drugs which are principally psychoactive and are abused almost exclusively by virtue and because of that property. All of these drugs can be described as either narcotics, stimulants, depressants, or hallucinogens."*
>
> *I don't believe there exists now any evidence to indicate that this class of drugs [anabolic steroids] possesses those properties, or at least there is very little evidence. So, I have some serious doubts as to whether the Controlled Substances Act is the appropriate piece of legislation to consider."*[6]

Therefore, an exception was carved out of the existing structure, which served to control AAS under the CSA, despite DEA stating that this was inappropriate and a poor match with the legislative intent of the original Act.

As such, with respect to the fact that AAS do not fit the CSA's criteria, nor its original legislative intent, it is especially inappropriate to apply DEA's proposed modifications under DEA-407 to the RHA with respect to this class of medication. The "one-size-fits-all" approach to regulating all controlled non-narcotic medication under the same rules is contradicted by the fact that AAS are ill-suited for inclusion under the CSA as a whole.

On 22 October 2004, President George W. Bush signed into law the Anabolic Steroid Control Act of 2004 ("ASCA 2004"), which became effective on January 20, 2005.[7] The 2004 Act raised the total number of anabolic steroids listed in Schedule III from twenty-five to fifty-nine.[8] The new Act also removed the prerequisite that the anabolic steroid possesses per se anabolic properties and made illegal the sale of most so-called "prohormones." In addition, Section 2(a) of the 2004 Act classified a drug or hormonal substance as an anabolic steroid if the following four criteria were met: (A) The substance is chemically related to testosterone; (B) the substance is pharmacologically related to testosterone; (C) the substance is not an estrogen, progestin, or a corticosteroid; and (D) the substance is not dehydroepiandrosterone (DHEA).[9] Therefore, hormones such as estrogen (the primary female sex hormone) are not controlled substances, while testosterone (the primary male sex hormone) is controlled under Schedule III of the CSA.

The new rules currently proposed by the DEA would therefore allow hormonal gender affirmation therapy transition therapy to commence and continue via telehealth without the second in-person examination for male to female transgender persons (transgender females). But a second visit within 30 days, with the prescribing physician, would be required for those transitioning from female to male (transgender males). This is due to the fact that testosterone is an AAS, and subject to the newly proposed rules, while estrogen is not controlled[10] and thus not

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[6] *Id.*
[7] *Id.*
[8] https://www.congress.gov/bill/108th-congress/senate-bill/2195/text
[9] https://www.regulations.gov/document?D=DEA-2011-0015-0001, at "Background Information"
[10] This is despite the fact that estrogen is known to be anabolic in multiple pathways. See: SHRIPAD B. DESHPANDE Shripad B. Deshpande, Neuroprotective Actions of Estrogen. Indian J Physiol Pharmacal 2000; 44(1). The anabolic properties of estrogen are well articulated and exploited in multiple domains, including animal husbandry where it is used alone or added to non-aromatizing AAS to produce an additive effect on anabolic

ensnared. To promote and ensure constitutionally guaranteed equal protection to similarly situated people undergoing gender affirmation through hormone therapy, DEA should exempt AAS like testosterone from the proposed regulatory structure.

Following ASCA 2004, on 18 December 2014, President Obama signed into law the Designer Anabolic Steroid Control Act ("DASCA"). DASCA was crafted to curtail the practice of synthesizing AAS that were designed to avoid control under the CSA through slight chemical modifications to existing structures. The Act also added 25 new substances to the existing list of steroids controlled under Schedule III, while granting additional powers to rapidly schedule emerging drugs that satisfy the definition set forth therein. Despite additional regulatory and scheduling control granted to DEA through DASCA, DEA has not found it necessary to promulgate new regulation or schedule additional AAS[11]. Additional restrictions on the telehealth market as regards AAS, are therefore unwarranted as the framework provided through ASCA, ASCA 2004, and DASCA have produced a foundation remarkably and demonstrably effective at preventing diversion.

III. Preventing Diversion and Promoting Access

a. Diversion is statistically irrelevant.

After enactment of ASCA, "*DEA virtually eliminated domestic sources of illicit steroid use*."[12] Diversion has been estimated to represent *significantly less than 5%* of the illegitimate AAS market[13]. However, even that relatively low figure appears to be a gross overestimate; a more accurate estimate would be under 1%. Operation TKO[14] (2003) resulted in the indictment and prosecution of the United States' biggest supplier of illicit AAS, Operation Gear Grinder[15] (2005) addressed the eight (remaining) largest suppliers, Operation Raw Deal[16] resulted in 124 arrests on various charges related to steroid distribution[17], and Operation Cyber Juice (2015) resulted in 90 arrests[18].

These operations each represent the largest steroid prosecutions executed since ASCA first took effect, and each represent the known majority suppliers of the contemporaneous illicit market[19].

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hormones and weight gain. See: Pampusch, M. S., White, M. E., Hathaway, M. R., Baxa, T. J., Chung, K. Y., Parr, S. L., Johnson, B. J., Weber, W. J., & Dayton, W. R. (2008). Effects of implants of trenbolone acetate, estradiol, or both, on muscle insulin-like growth factor-I, insulin-like growth factor-I receptor, estrogen receptor-{alpha}, and androgen receptor messenger ribonucleic acid levels in feedlot steers. *Journal of animal science*, *86*(12), 3418–3423. https://doi.org/10.2527/jas.2008-1085

[11] Human Enhancement Drug Matters. Theme: Enhancement Drugs and the Criminal Justice System. 2652-9572 (Online), Volume 5, Issue 1. August 2022.

[12] https://www.dea.gov/sites/default/files/2021-04/1990-1994_p_67-76.pdf

[13] William Llewellyn and Ronny Tober. Underground Anabolics. Body of Science, 2010.

[14] https://en.wikipedia.org/wiki/Operation_TKO

[15] https://abcnews.go.com/US/LegalCenter/story?id=1411333

[16] https://www.justice.gov/archive/opa/pr/2007/September/07_crm_753.html

[17]: https://www.nytimes.com/2007/09/29/sports/baseball/29doping.html

[18] https://www.dea.gov/press-releases/2015/09/01/dea-announces-major-steroid-operation

[19] https://www.nytimes.com/2007/09/29/sports/baseball/29doping.html

By 2005 DEA stated that over 80% of seized black market AAS originated in Mexico[20]. None of these investigations resulted in the discovery of AAS produced by legitimate facilities (whether compounding pharmacies or pharmaceutical firms), and later diverted its focus to the illegitimate market. Operations TKO and Gear Grinder, respectively, prosecuted veterinary labs located in Mexico, while Operations Raw Deal and Cyber Juice prosecuted domestic underground labs. The largest AAS prosecutions to follow their becoming controlled substances have belied the conclusion that diversion of otherwise legitimate AAS represented a significant portion of the illicit market.[21]

Moreover, a five-year survey of anabolic steroid cases in United States district courts[22] from 2013-2017 did not find diversion to be the primary source of illegal AAS purchases. Of the 63 cases totalling 184 defendants, prosecuted in in 41 district courts, 27 involved the importation of raw steroid powder from China. In 2 cases, the steroids were obtained from Turkey. In the remaining cases Bulgaria, Canada, Israel, Pakistan, Poland, Romania, Singapore, Thailand, and the United Kingdom were the originating source of the illegally-purchased AAS[23]. In addition, no legitimate online pharmacies were implicated, but rather online marketplaces such as Silk Road and Evolution Marketplace. The spectre of diversion is simply not proportional to the imposed regulations under DEA-407, as the existing controls have effectively eliminated this threat.

But note that although anabolic steroids are controlled substances in the United States, this is not the case worldwide. Overseas the sale of AAS is often unrestricted, leading to their widely available status, oftentimes legally and without a prescription (e.g., they are "over the counter" medications).[24,25] Therefore, while a foreign pharmacy may run afoul of United States law, or even international law, when they ship AAS outside of their country of origin, they are often in compliance with their own domestic regulations. Most of the illicit hormone products in the European market come from EU-based distributors or Russia, but also from many of the same sources illegally supplying the United States market, such as Thailand, Turkey, Egypt, India and Pakistan[26]. Placing additional barriers on prescribing physicians within the United States are unnecessary to prevent diversion and can not be expected to have an impact on the illicit market.

Since the removal of methandrostenolone from the United States, the majority of illicit AAS had come from Mexico (as seen through Operation TKO and Gear Grinder) as well as other countries

[20] https://www.legistorm.com/stormfeed/view_rss/385816/organization/95775/title/dea-leads-largest-steroid-bust-in-history-82-percent-of-all-dea-seized-and-analyzed-steroids-in-us-are-manufactured-in-mexico-large-majority-of-those-come-from-targets-in-operation-gear-grinder.html

[21] But note that immediately prior to ASCA, increased FDA regulation resulted in lowered diversion, while foreign actors such as Laboratorios Milanos de Mexico began smuggling AAS such as the now-discontinued Dianabol into the United States.

[22] Denham, B. E. (2019). Anabolic Steroid Cases in United States District Courts (2013–2017): Defendant Characteristics, Geographical Dispersion, and Substance Origins. *Contemporary Drug Problems*, *46*(1), 41–57.

[23] The one prosecution that arguably involved domestic distribution was the Biogenesis case, in which the prescribing doctor was educated in Belize and did not have a valid license to practice medicine in the United States. Given these circumstances, the proposed rules amending the RHA would not have prevented this act.

[24] Cramer RJ. Anabolic steroids are easily purchased without a prescription and present significant challenges to law enforcement officials 2005.

[25] Hermansson G. Doping trade: business for the big ones 2002. In: Play the Game

[26] Id.

such as Russia, Romania and Greece[27]. Now, the majority of AAS is likely to be produced by underground labs using raw powder obtained from Chinese sources (as seen through Operation Raw Deal and Cyber Juice). Note that many of these countries are the same as listed in the five-year survey, and that none of these countries, nor the European Union are thought to receive diverted AAS originating from the United States.

In 2019, the year immediately preceding the PHA and current telehealth prescribing regulations, a total of 2,916 drug reports were identified by the DEA's National Forensic Laboratory Information System (NFLIS) drug laboratories as AAS, representing less than 1% of all drug reports[28]. In 2020, after the ongoing PHE was officially declared and the new telehealth regulations took effect, NFLIS noted a drop in that number, to 2130 identified AAS, again less than 1%[29]. In 2021, the last year for which annual data is available, that number decreased a second time, to 1904[30]. Therefore, under the current regulations illegal use of AAS has steadily fallen.

While preventing the illicit sale and use of AAS may rightly be a compelling government interest, the proposed rules are not tailored to furthering that goal. There is no cause to believe that the illicit market will be impacted in any way, nor those goals achieved, through implementation of the rules addressed herein. The DEA's data clearly indicated a downward trend under the current regulations, with no cause to believe this trend will not continue. The proposed rules are overly cumbersome and serve only to add restrictions to a domestic market that is simply not a contributory factor in the illicit sale of AAS.

b. Data Indicates That There Are Too Few AAS Prescriptions

Although AAS prescriptions, specifically testosterone, have been displaying an upward trend[31, 32] over the past two decades, this is not without obvious cause. There has been a decline in mean total testosterone levels over the past two decades and total testosterone levels are trending progressively lower with a concurrent rise in body mass index. This has been most noticeable for adolescent and young adult males, in whom 20% currently suffer from testosterone deficiency[33].

There has been an obvious and substantial age-independent decline in testosterone that does not appear to be attributable to observed changes in explanatory factors, including health and lifestyle characteristics such as smoking and obesity. This decline in testosterone levels have far exceeded the generally estimated population-level declines and are greater in magnitude than the cross-sectional declines in testosterone that would typically be associated with age. These results

[27] Cramer RJ.Anabolic steroids are easily purchased without a prescription and present significant challenges to law enforcement officials 2005. Available atdated 3 November 2005.
[28] https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-DRUG_2019_Annual_Report.pdf
[29] https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLISDrug2020AnnualReport.pdf
[30] https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLISDrug_2021AnnualReport.pdf
[31] Baillargeon J, Kuo Y, Westra JR, Urban RJ, Goodwin JS. Testosterone Prescribing in the United States, 2002-2016. *JAMA.* 2018;320(2):200–202.
[32] Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med.* 2013;173(15):1465-1466.
[33] Lokeshwar, S. D., Patel, P., Fantus, R. J., Halpern, J., Chang, C., Kargi, A. Y., & Ramasamy, R. (2021). Decline in Serum Testosterone Levels Among Adolescent and Young Adult Men in the USA. *European urology focus*, *7*(4), 886–889.

indicate that recent years have seen a substantial, and yet unrecognized, age-independent population-level testosterone decrease in American men[34].

While the prescribing data and increasing number of AAS prescriptions has produced consternation in some, the actual numbers tell a different story; annual prescriptions for testosterone are not rising at the same pace as testosterone deficiency. Far more men, including those of an increasingly younger age bracket, are suffering from clinically low testosterone levels than there are men being appropriately treated with testosterone replacement therapy. By requiring both the examining doctor and the prescribing doctor to have DEA licenses (despite only one writing the prescription), the new rule will reduce the number of doctors who can participate in the TRT/HRT practice of telehealth. In addition, implementing the 30-day rule, will cause logistical and administrative burden thus reduce the number of patients who receive appropriate care. This is not compatible with the rising need for testosterone and other AAS necessary to ensure appropriate treatment is available to those who are (and will be) in need.

c. Ongoing Administrative Burdens and Physician Shortages

The United States projected to have a physician shortage of between 37,800 and 124,000 physicians within the next 11 years[35]. This includes between 17,800 and 48,000 primary care physicians and between 21,000 and 77,100 non-primary care physicians. These predictions, already underway, will increase barriers to care, especially in populations already underserved by the health system and result in health care-use patterns that leave the most vulnerable populations at risk.

By adding additional administrative burdens such as dual recordkeeping, tandem two-way interactive video calls for each patient (as proposed under the new RHA rulemaking) the physician shortage will not be ameliorated by telehealth, but rather impeded by doubling the workload of each physician.

IV. Safety Profile of Anabolic Androgenic Steroids

A search of medical databases from 1975 through 2014 revealed no deaths until 1990 and a total of 19 fatal cases between 1990 and 2012. These are limited to cases in which the autopsy excluded in all cases, extracardiac causes of death[36]. Therefore, in 39 years, only 19 cases that could be directly attributed to AAS use appeared in the medical literature, or less than a single death every other year. In 6 of the 19 cases, there were no AAS found in the deceased through a post-mortem forensic analysis, but rather use was ascertained through interviews with friends and family who provided anecdotal information that the deceased had used AAS. The safety

[34] Travison, T. G., Araujo, A. B., O'Donnell, A. B., Kupelian, V., & McKinlay, J. B. (2007). A population-level decline in serum testosterone levels in American men. *The Journal of clinical endocrinology and metabolism*, *92*(1), 196–202.

[35] The Complexities of Physician Supply and Demand: Projections From 2019 to 2034 (PDF), Association of American Medical Colleges (AAMC).

[36] Frati, P., Busardò, F. P., Cipolloni, L., Dominicis, E. D., & Fineschi, V. (2015). Anabolic Androgenic Steroid (AAS) related deaths: autoptic, histopathological and toxicological findings. *Current neuropharmacology*, *13*(1), 146–159.

profile of anabolic steroids is among (if not the absolute) best of any class of pharmaceutical. Combined with the fact that they are not being diverted from legitimate sources (those impacted by the proposed rules), weighs heavily against their being subject to a 30-day re-examination of the patient before a refill can be prescribed.

V. The Ryan Haight Act

The *Ryan Haight* Online Pharmacy Consumer Protection *Act* of 2008 was enacted to address the emerging problem of internet pharmacies selling controlled substances online. The Act was named for Ryan Haight, a teenage boy who in December of 2003, without a valid prescription or a legitimate doctor-patient relationship, obtained hydrocodone from an online pharmacy and ingested a lethal dose. The Act took effect on 13 April 2009, and set forth requirements for online pharmacies, most importantly that a valid prescription and legitimate doctor-patient relationship was required to dispense controlled substances.

Although the internet is the primary source for illicit steroid purchases[37], domestic prescriptions, whether telehealth or otherwise, are not implicated in that market. Neither are domestic pharmacies. The available data strongly indicates that the primary source are rogue pharmacies located offshore, and not within the United States, none of whom require a prescription (nor be affected by the instant rulemaking). A 2018 study titled "*The Availability and Acquisition of Illicit Anabolic Androgenic Steroids and Testosterone Preparations on the Internet*[38]," found that of the top ten most visible internet pharmacies offering anabolic steroids, all were foreign with none located within the United States. Increasing barriers to domestic prescription of AAS through telehealth would not result in reduced diversion or decreased availability to the black market, but rather exclusively the legitimate market.

Perhaps most importantly, the tragic circumstances that resulted in Ryan Haight's death and namesake Act would not have been altered if the proposed rules had been in place. He did not receive a prescription from a telehealth doctor nor did he receive his medication from a legitimate online pharmacy (as the subsequent criminal prosecution proved). Ryan Haight did not die from an overdose of the types of medication implicated in the new rules. Implementing rules that greatly restrict telehealth and encumber prescription of non-narcotic controlled substances do not achieve the ultimate goal of the RHA.

VI. Populations and Medical Conditions

The regulations proposed under DEA-407 will impact numerous populations suffering from a variety of afflictions. Below is a non-exhaustive list containing a few of these populations who are typified by testosterone insufficiency or deficiency and listing several conditions that are

[37] Perry PJ, Lund BC, Deninger MJ, Kutscher EC, Schneider J. Anabolic steroid use in weightlifters and bodybuilders: An internet survey of drug utilization. Clin J Sport Med. 2005;15:326–330

[38] McBride, J. A., Carson, C. C., 3rd, & Coward, R. M. (2018). The Availability and Acquisition of Illicit Anabolic Androgenic Steroids and Testosterone Preparations on the Internet. *American journal of men's health*, *12*(5), 1352–1357. https://doi.org/10.1177/1557988316648704

characterized by testosterone deficiency, for which testosterone and other anabolic androgenic steroids for either primary, secondary, or adjunct therapy.

a. Veterans

Mental health disorders including posttraumatic stress disorders (PTSD) and major depressive disorders manifest with greater frequency in veterans when compared to the non-military population[39,40,41]. There is a strong correlation between those maladies and the frequent incidence of pituitary insult resulting from repeated subconcussive blasts and other factors leading to Traumatic Brain Injury (TBI) and mild Traumatic Brain Injury (mTBI)[42]. These types of injuries are known to result in posttraumatic hypopituitarism (PTHP)[43]. As a result, these conditions, thought to be originating with pituitary insult[44], and symptoms characteristic of both PTHP and PTSD, can be linked to pituitary dysfunction, and accordingly may be amenable to treatment with hormone replacement[45]. However, despite a well-articulated and successful treatment protocol, lack of access to medical services contributes to the high suicide rate among veterans[46].

From 2007 to 2011, the number of AAS prescriptions for men (99% of total) increased more than two-fold in the military, with the 99% of those prescriptions going to men and with 35- to 44-year-olds accounting for the greatest increase. This far surpassed the rate seen in the general public[47], and reflects the specific needs of the military population. Some, though not all, of these needs are met through Veterans services provided by the VA, which include telehealth outreach[48]. However, some veterans prefer to utilize private doctors and specialists that are readily available through telehealth, though not by location. As the veteran community is among the most in dire need of testosterone replacement therapy, putting restraints on telehealth would be a disproportionate burden on this group. Requiring multiple visits and additionally requiring that both practitioners are required to have a current DEA license places undue burden on

[39] Seal, K. H., Bertenthal, D., Miner, C. R., Sen, S., & Marmar, C. (2007). Bringing the war back home: mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs facilities. *Archives of internal medicine*, *167*(5), 476–482.

[40] Byers, A. L., & Yaffe, K. (2014, 2014/06/01/). Depression and dementias among military veterans. Alzheimer's & Dementia, 10(3, Supplement), S166-S173.

[41] Richardson, L. K., Frueh, B. C., & Acierno, R. (2010, Jan). Prevalence estimates of combat-related post-traumatic stress disorder: critical review. Aust N Z J Psychiatry, 44(1), 4-19.

[42] Vartanian, O., Tenn, C., Rhind, S. G., Nakashima, A., Di Battista, A. P., Sergio, L. E., Gorbet, D. J., Fraser, D. D., Colantonio, A., King, K., Lam, Q., Saunders, D., & Jetly, R. (2020). Blast in Context: The Neuropsychological and Neurocognitive Effects of Long-Term Occupational Exposure to Repeated Low-Level Explosives on Canadian Armed Forces' Breaching Instructors and Range Staff. Frontiers in neurology, 11, 588531. https://doi.org/10.3389/fneur.2020.588531

[43] Wilkinson, C. W., Pagulayan, K. F., Petrie, E. C., Mayer, C. L., Colasurdo, E. A., Shofer, J. B., Hart, K. L., Hoff, D., Tarabochia, M. A., & Peskind, E. R. (2012). High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. *Frontiers in neurology*, *3*, 11.

[44] Id.

[45] Id.

[46] Hester, R. D. (2017, 2017/08/18). Lack of access to mental health services contributing to the high suicide rates among veterans. International Journal of Mental Health Systems, 11(1), 47.

[47] Canup, R., Bogenberger, K., Attipoe, S., Jones, D. R., Olsen, C. H., Stephens, M. B., & Deuster, P. A. (2015). Trends in Androgen Prescriptions From Military Treatment Facilities: 2007 to 2011. *Military medicine*, *180*(7), 728–731.

[48] https://www.research.va.gov/research_in_action/Telehealth-outreach-for-PTSD.cfm

veterans, especially in light of the fact that they may be, or have been, relocated to multiple parts of the country as a consequence of their service.

Depending on the particular specialty of veterans, they may be subject to greater risk than the overall veteran community for the aforementioned pituitary and hypothalamic impact[49]. Specifically, the highly intensive operational training and combat deployment of special operation forces (SOF) create a constellation of maladies[50] either adversely affecting or being caused because of adverse effect on the Hypothalamic-Pituitary-Gonadal Axis, resulting in significantly decreased testosterone levels[51]. This group also suffers from drastically increased risk for work-related injuries such as the aforementioned TBI and mTBI[52], which again adversely affect endocrine function[53], with the most frequent deficiency disorders being low growth hormone and hypogonadism[54], both of which are greatly pronounced in the SOF community.

The symptoms often include endocrine imbalances (such as low testosterone and growth hormone); insomnia; chronic pain; substance dependence; anxiety and stress; poor social relationships; sexual dysfunction; and cognitive impairments. Suicide rates amongst US special operation forces are also the highest in the military (about 30% higher than the US military)[55]. Many of these symptoms are consistent with endocrine dysfunction and hormone deficiencies for which hormone replacement (AAS) therapy is front-line treatment. Telehealth is a readily available source for this treatment and currently serving both the veteran and SOF community but would be adversely impacted by the proposed rule to restrict prescription of non-narcotic controlled substances.

Other barriers for accessing services are travel distance to services; lack of confidence in health services; financial issues; and worries about privacy[56]. Adding to this is that due to the unique physical and mental health needs of SOF veterans most existing health services are not suitable

[49] Wang, Z., Wilson, C. M., Ge, Y., Nemes, J., LaValle, C., Boutté, A., Carr, W., Kamimori, G., & Haghighi, F. (2020). DNA Methylation Patterns of Chronic Explosive Breaching in U.S. Military Warfighters. *Frontiers in neurology*, *11*, 1010.

[50] Frueh, B. C., Madan, A., Fowler, J. C., Stomberg, S., Bradshaw, M., Kelly, K., Weinstein, B., Luttrell, M., Danner, S. G., & Beidel, D. C. (2020, Jul). "Operator syndrome": A unique constellation of medical and behavioral health-care needs of military special operation forces. Int J Psychiatry Med, 55(4), 281-295.

[51] Linderman, J. K., O'Hara, R., & Ordway, J. (2020). Effect of Special Operations Training on Testosterone, Lean Body Mass, and Strength and the Potential for Therapeutic Testosterone Replacement: A Review of the Literature. Journal of special operations medicine : a peer reviewed journal for SOF medical professionals, 20(1), 94–100.

[52] Edlow, B. L., Bodien, Y. G., Baxter, T., Belanger, H. G., Cali, R. J., Deary, K. B., Fischl, B., Foulkes, A. S., Gilmore, N., Greve, D. N., Hooker, J. M., Huang, S. Y., Kelemen, J. N., Kimberly, W. T., Maffei, C., Masood, M., Perl, D. P., Polimeni, J. R., Rosen, B. R., Tromly, S. L., … Dams-O'Connor, K. (2022). Long-Term Effects of Repeated Blast Exposure in United States Special Operations Forces Personnel: A Pilot Study Protocol. *Journal of neurotrauma*, *39*(19-20), 1391–1407.

[53] Izzy, S., Chen, P. M., Tahir, Z., Grashow, R., Radmanesh, F., Cote, D. J., Yahya, T., Dhand, A., Taylor, H., Shih, S. L., Albastaki, O., Rovito, C., Snider, S. B., Whalen, M., Nathan, D. M., Miller, K. K., Speizer, F. E., Baggish, A., Weisskopf, M. G., & Zafonte, R. (2022). Association of Traumatic Brain Injury With the Risk of Developing Chronic Cardiovascular, Endocrine, Neurological, and Psychiatric Disorders. JAMA network open, 5(4), e229478.

[54] Wilkinson, C. W., Pagulayan, K. F., Petrie, E. C., Mayer, C. L., Colasurdo, E. A., Shofer, J. B., Hart, K. L., Hoff, D., Tarabochia, M. A., & Peskind, E. R. (2012). High prevalence of chronic pituitary and target-organ hormone abnormalities after blast-related mild traumatic brain injury. Frontiers in neurology, 3, 11.

[55] SOCOM. (2020). Psychological Autopsy Study of Suicides among US Special Operations Forces.

[56] Cheney, A. M., Koenig, C. J., Miller, C. J., Zamora, K., Wright, P., Stanley, R., Fortney, J., Burgess, J. F., & Pyne, J. M. (2018, 2018/07/31). Veteran-centered barriers to VA mental healthcare services use. BMC Health Services Research, 18(1), 591.

to meet the need of this group. Due to the unique and increased need for this population, and the high degree of medical specialization required to adequately meet their needs, specialists are not widely available. The use of telehealth is currently, and would continue to be, an option to ameliorate this need, but the proposed regulations would adversely impact its efficacy and practicality.

b. Transgender Populations

Both transgender men and women utilize hormone therapy as part of the transition process. Testosterone therapy is used in transgender men to produce male primary and secondary sexual characteristics and to suppress physical features that would be considered traditionally feminine. The administration of exogenous virilizing hormones is considered medically necessary for many transgender individuals[57].

But in transgender women, exogenous estrogen is preferred used to help feminize patients, and anti-androgens are used as adjuncts to help suppress masculinizing features[58]. Overall, the number of transgender individuals pursuing one of the two forms of hormone therapy has risen over the years[59].

Within the first 6 months of hormone therapy, estrogen combined with androgen blockers in transgender females begin to induce breast growth, decreased testicular volume, and decreased and spontaneous erections. Within the first six months of utilization of testosterone and/or other AAS, changes in transgender males begin to manifest with a deepening voice, the cessation of menses, breast atrophy, and clitoral enlargement. In both transgender females and males body fat and muscle mass changes occur. However, the desired result is typically not achieved until several years after hormone therapy has commenced[60]. Testosterone therapy for gender affirmation is not discontinued, but rather continued lifelong[61]. Considering these facts, the 30-day rule seems overly burdensome on both patient and physician. A more reasonable rule would extend the in-person requirement to a 90-day or 180-day timeline.

Regardless of allotted time, the new rules promulgated through DEA-407, only transgender males will be required to fulfil the 30-day requirement, while transgender females will not. It must be noted that the desired physiological changes for the male transgender patient are only achievable through testosterone, and there is no currently existing alternative therapy that can produce similar results. The disparate treatment of male versus female transgender people warrants reconsideration of the rule, in accordance with equal protection.

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[57] World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. 7th ed; 2011.

[58] Unger C. A. (2016). Hormone therapy for transgender patients. *Translational andrology and urology*, *5*(6), 877–884.

[59] Leinung MC, Urizar MF, Patel N, et al. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract 2013;19:644-50. 10.4158/EP12170.OR

[60] Smith, K. P., Madison, C. M., & Milne, N. M. (2014). Gonadal suppressive and cross-sex hormone therapy for gender dysphoria in adolescents and adults. *Pharmacotherapy*, *34*(12), 1282–1297.

[61] Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People. 7th Version. World Professional Association for Transgender Health.

Finally, medical care for transgender people is a highly specialized field incorporating a multidisciplinary approach to care[62]. It is not the case that all transgender persons will live near (or even within driving distance) of the specialists necessitated by the requisite standard of care. Some transgender people live in states that are increasingly restricting access to gender-affirming care. Telehealth bridges this geographical gap, but the proposed rule will serve as a significant barrier to access appropriate care.

c. HIV(+)

Low testosterone levels are common in both men and women with human immunodeficiency virus (HIV) infection and may contribute to loss of lean body mass and AIDS wasting. Causes of low testosterone levels are complex and may include chronic illness, HIV infection and its complications, medications used to treat HIV and opportunistic diseases, and normal aging-related declines[63]. Testosterone therapy and FDA-approved androgens have been used successfully in HIV-infected men and women presenting with weight loss and low testosterone, with the goal of curtailing weight loss and promoting lean mass gain[64]. HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities and gay/bisexual men[65]. Therefore, under the newly proposed rule, the infected population will disproportionately affect those constitutionally protected classes.

HIV-infected men are affected by increased incidence of testosterone deficiency, which is aggravated as they progress to AIDS. In addition to the lean mass and body weight gains experienced by hypogonadal HIV+ men administered testosterone, it is worth noting that they also experience improvements in energy and mood. All of these gains result in a greater quality of life[66] in the affected population.

Morbidity and mortality are both exacerbated by weight loss in HIV+ patients. Testosterone therapy has been shown through metanalysis to not only increase the aforementioned lean body mass but also total body weight. Additionally, testosterone therapy produces functional exercise capacity and perceived quality of life in patients with HIV wasting syndrome, including the amelioration of numerous adverse effects.[67]

Although there is arguably a comparable occurrence of testosterone deficiency in men living with HIV compared to non-infected controls, dysfunction related to hypogonadism is more

[62] Chen, S., & Loshak, H. (2020). *Primary Care Initiated Gender-Affirming Therapy for Gender Dysphoria: A Review of Evidence Based Guidelines*. Canadian Agency for Drugs and Technologies in Health.

[63] Dobs A. (2003). Role of testosterone in maintaining lean body mass and bone density in HIV-infected patients. *International journal of impotence research, 15 Suppl 4,* S21–S25.

[64] Shalender Bhasin, Juan P Brito, Glenn R Cunningham, Frances J Hayes, Howard N Hodis, Alvin M Matsumoto, Peter J Snyder, Ronald S Swerdloff, Frederick C Wu, Maria A Yialamas, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744,

[65] https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics/

[66] Cofrancesco, J., Jr, Whalen, J. J., 3rd, & Dobs, A. S. (1997). Testosterone replacement treatment options for HIV-infected men. *Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association*, *16*(4), 254–265.

[67] Kong, A., & Edmonds, P. (2002). Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. *The Lancet. Infectious diseases*, *2*(11), 692–699.

pronounced in the infected population, who experience a higher burden of symptoms[68]. In the majority of studies addressing the use of testosterone treatment in HIV-infected patients, testosterone has been found to help prevent loss of lean body and muscle mass. In addition to its effects on body composition, testosterone therapy results in improved mood, libido, and bone mineral density[69]. The effects on bone mineral density are especially important since the HIV-infected population has increased rates of osteoporosis and fracture compared to HIV-uninfected men[70].

d. Spinal Cord Injuries

Testosterone deficiency is often manifested in spinal cord injuries ("SCI"). This can serve to increase the risk of testosterone deficiency and thereby result in unfavorable body composition changes and loss of function. Metanalysis of testosterone therapy with exercise has been shown to improve functionality (including physical strength and capacity), body composition (through an increase in muscle mass), cardiac and bone health, and energy expenditure, in men with SCI[71]. Due to the nature of this injury producing immobility, and the efficacy of testosterone therapy as an adjunct, it is unreasonable to require a visit within 30-days of a testosterone or AAS prescription.

e. Sarcopenia and Osteoporosis

In older people, Osteoporosis and sarcopenia are the most common musculoskeletal disorders. Osteoporosis is characterized by reduced bone mass and deterioration of bone tissue. People with osteoporosis are at increased risk for bone fracture. Sarcopenia is characterized by the loss of muscle mass, strength, and function. These two conditions often manifest in tandem. Hypogonadism is associated with both sarcopenia and osteoporosis and appears to play an important role in its pathogenesis.[72] Accordingly, bone and muscle loss often accompany testosterone deficiency. While it is widely understood that testosterone is anabolic in muscle tissue, it has a downstream anabolic effect on bone tissue after metabolization (through aromatase) to estrogen. Thus, because estrogen is the primary regulator of the male skeleton, and the primary source of estrogen in males is aromatized testosterone, low testosterone is often the causative factor in osteoporosis.[73,74,75]

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[68] Postel, N., Wolf, E., Balogh, A., Obermeier, M., Degen, O., Mayr, C., Baumgarten, A., Pauli, R., Mueck, B., Jaeger, H., & Noe, S. (2021). Functional Hypogonadism and Testosterone Deficiency in Aging Males With and Without HIV-infection. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*, *129*(11), 798–802.

[69] Dobs A. (2003). Role of testosterone in maintaining lean body mass and bone density in HIV-infected patients. *International journal of impotence research*, *15 Suppl 4*, S21–S25.

[70] Grant, P. M., Li, X., Jacobson, L. P., Palella, F. J., Jr, Kingsley, L. A., Margolick, J. B., Dobs, A. S., Lake, J. E., Althoff, K. N., & Brown, T. T. (2019). Effect of Testosterone Use on Bone Mineral Density in HIV-Infected Men. *AIDS research and human retroviruses*, *35*(1), 75–80.

[71] McLoughlin, R. J., Lu, Z., Warneryd, A. C., & Swanson, R. L., 2nd (2023). A Systematic Review of Testosterone Therapy in Men With Spinal Cord Injury or Traumatic Brain Injury. *Cureus*, *15*(1), e34264.

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[73] Barrett-Connor E, Mueller JE, von Muhlen DG et al. (2000) Low levels of estradiol are associated with vertebral fractures in older men, but not women: the Rancho Bernardo Study. J Clin Endocrinol Metab 85:219–223.

f. Clinically Obese and Diabetic

Obesity has been steadily increasing[76,77] in past decades. The CDC reports that obesity-prevalence is 39.8% among adults aged 20 to 39 years, 44.3% among adults aged 40 to 59 years, and 41.5% among adults aged 60 and older. Obesity impacts quality of life and shortens life expectancy. Obesity is a chronic condition that is difficult to treat with lifestyle or behavioral intervention alone[78].

Obesity is associated with numerous comorbidities and is a contributory factor contributes to insulin resistance, type 2 diabetes (T2DM). Lifestyle changes are necessary but not sufficient in most to produce weight loss[79,80].

Testosterone therapy increases lean body mass commensurate with elevation of resting energy expenditure. In addition, testosterone therapy in obese men (both with and without diet and increased physical activity) reduced total fat mass while improving cardiovascular and metabolic function[81,82,83] while higher testosterone levels can significantly decrease the risk of type 2 diabetes in men[84].

g. Aneroxa Nervosa

Anorexia nervosa is a psychiatric disorder associated with global endocrine dysregulation, and preferentially affects adolescent girls and women[85]. It is characterized by altered body image, persistent food restriction and low body weight. This dysfunction of the hypothalamic-pituitary axis includes hypogonadotrophic hypogonadism with relative androgen deficiency, growth

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[74] Khosla S, Melton LJ III, Atkinson EJ et al. (1998) Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 83:2266–2274.

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[76] https://www.cdc.gov/obesity/data/adult.html

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[78] Taubes G. Treat obesity as physiology, not physics. Nature 2012; 492:155.

[79] Colagiuri S. Diabesity: therapeutic options. Diabetes Obes Metab 2010; 12:463–473.

[80] Henry RR, Chilton R, Garvey WT. New options for the treatment of obesity and type 2 diabetes mellitus (narrative review). J Diabetes Complications 2013; 27:508–518.

[81] Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. Int J Endocrinol 2014; 2014:527470.

[82] Francomano D, Bruzziches R, Barbaro G, et al. Effects of testosteroneundecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: a pilot study. J Endocrinol Invest 2014; 37:401–411.

[83] Yassin A, Doros G. Testosterone therapy in hypogonadal men results in sustained and clinically meaningful weight loss. Clin Obes 2013; 3:73–83.

[84] Yao, Q. M., Wang, B., An, X. F., Zhang, J. A., & Ding, L. (2018). Testosterone level and risk of type 2 diabetes in men: a systematic review and meta-analysis. *Endocrine connections*, *7*(1), 220–231.

[85] As this is the case, it is discussed again below, where women and hormone replacement therapy are discussed at greater length

hormone resistance, hypercortisolaemia, non-thyroidal illness syndrome, hyponatraemia, and hypooxytocinaemia.[86]

VI. Hormone Deficiency

a. Men

It is well recognized that aging in men is accompanied by a decline in the serum levels of some adrenal and testicular steroids. This decrease is thought to negatively affect many physiological processes during aging.[87] Testosterone deficiency is thought to range from 2-10%, worldwide[88].

Testosterone replacement therapy in the aging male has been shown to have a beneficial effect on muscle and fat mass as well as on bone mineral density. Epidemiological data shows an inverse relationship between testosterone levels and obesity, insulin resistance, the metabolic syndrome and type 2 diabetes mellitus. [89]

Current and recommended best practices for prescribing testosterone are to evaluate factors such as patient preference, pharmacokinetics, formulation-specific adverse effects, treatment burden, and cost, which should all be taken into account when evaluating the proper course of testosterone replacement. A standardized plan of monitoring should include evaluating symptoms, adverse effects, and compliance; measuring serum T and hematocrit concentrations; and evaluating additional risk during the first year after initiating T therapy[90]. For prescriptions of testosterone and other androgens, the mandated second visit within 30 days is overly burdensome and contradicts the underlying core rationale of telemedicine—that increased accessibility through technology will reduce barriers to effective care. Data produced within 30 days of beginning hormone therapy will be negligible at best, while greatly inconveniencing the patient with a visit that could have been a phone call, video conference, or lab work. Requiring a physician appointment within 30 days conflicts with clinical guidelines established by multiple medical associations including the American Urological Association (AUA), Endocrine Society (ES), and International Society of Sexual Medicine (ISSM). The follow-up requirements for testosterone replacement therapies range from 3 months to 6 months to once or twice per year on maintenance therapy.[91]

Through the new restrictions imposed by DEA-407, the cost of patient care will rise by adding a required visit within 30 days of the first prescription. There is little to no medical basis for such a

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[86] Schorr, M., & Miller, K. K. (2017). The endocrine manifestations of anorexia nervosa: mechanisms and management. *Nature reviews. Endocrinology*, *13*(3), 174–186.

[87] Bélanger, A., Candas, B., Dupont, A., Cusan, L., Diamond, P., Gomez, J. L., & Labrie, F. (1994). Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. *The Journal of clinical endocrinology and metabolism*, *79*(4), 1086–1090.

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[89] Nigro, N., & Christ-Crain, M. (2012). Testosterone treatment in the aging male: myth or reality?. *Swiss medical weekly*, *142*, w13539.

[90] Bhasin, S., Brito, J. P., Cunningham, G. R., Hayes, F. J., Hodis, H. N., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Wu, F. C., & Yialamas, M. A. (2018). Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism*, *103*(5), 1715–1744.

[91] Pelzman, D. L., & Hwang, K. (2020). Testosterone therapy: where do the latest guidelines agree and differ?. *Current opinion in endocrinology, diabetes, and obesity*, *27*(6), 397–403.

visit. Due to the outstanding safety profile of testosterone and many other AAS, such a rapid in-person (re)evaluation is unwarranted and serves only to impose additional expenditure for treatment (including not only the cost of the visit itself but travel expenses), but also duplicative record keeping, and an added administrative burden on both the prescribing physician and the original examining physician (who is now forced to keep records from which they are entirely removed otherwise).

The new 30-day requirement is scientifically unsound in as much as this is less than the requisite time for numerous long-acting HRT modalities to achieve steady state concentration[92]. Negligible worthwhile data is going to present by this timepoint. A bare minimum time by which to examine and evaluate a course of treatment involving testosterone and other AAS would be 90-180 days, to allow the hormone to reach a steady level and impart effects that would be cognizable in lab work or a physical examination.

The 30-day also raises a question that necessitates clarification. Utilizing many of the longer acting – and convenient – options for HRT and TRT could now be impermissible. For example, testosterone pellets are administered in a bolus dose that provides eugonadal testosterone levels for three (3) to six (6) months[93]. Theoretically a single administration would be a 90-day supply of medication. Injectable testosterone undecanoate, a long-acting form of testosterone, is administered in a bolus dose that provides eugonadal testosterone levels for ten (10) to 14 weeks. Both of these forms of testosterone, preferred by many due to the infrequency of administration, would now appear to be off the table as a treatment modality for the initial prescription. Clarification on this rule would be greatly appreciated, because as written it appears to not only restrain the initial prescription to 30 days, but also to proscribe specific drugs depending on presentation.

The impact of direct-to-consumer telehealth on the field of urology is vast and continues to grow[94], but under the proposed rules, the growth of this industry will not meet the increasing demand for care.

b. Women

Serum testosterone levels in women decline with age, with the largest decrease occurring before menopause [95,96]. Endogenous testosterone plays a crucial role in women's health, both through direct androgenic action and antecedent to conversion by the aromatase enzyme to estrogen[97]. This decrease in serum testosterone levels can result in decreased bone mineral density, sarcopenia (age-related decline in muscle), and decreased libido. Decreased libido is also

[92] Typically four (4) to five (5) half-lifes. See generally: Wadhwa RR, Cascella M. Steady State Concentration. [Updated 2022 Mar 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.

[93] McCullough A. (2014). A Review of Testosterone Pellets in the Treatment of Hypogonadism. *Current sexual health reports*, *6*(4), 265–269. https://doi.org/10.1007/s11930-014-0033-7

[94] Jesse, E., Thirumavalavan, N., & Loeb, A. (2022). Increase in Direct-to-Consumer Telehealth in Urology. *Current sexual health reports*, *14*(4), 119–127

[95] Baillargeon, J., Urban, R. J., Raji, M. A., Westra, J. R., Williams, S. B., Lopez, D. S., & Kuo, Y. F. (2020). Testosterone Prescribing Among Women in the USA, 2002-2017. *Journal of general internal medicine*, *35*(6), 1891–1893.

[96] Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab. 2005;90(7):3847–3853.

[97] Simpson ER, Davis SR. Minireview: aromatase and the regulation of estrogen biosynthesis--some new perspectives. Endocrinology. 2001;142(11):4589–4594. doi: 10.1210/endo.142.11.8547.

common after menopause[98], bilateral oophorectomy[99,100], and numerous conditions that disturb the production of androgens[101].

The total number of women prescribed testosterone therapy has varied by year, but TRT has become an increasingly accepted as a treatment modality for women. In a recent study, testosterone alone was shown to be prescribed to women at nearly half the rate of estrogen/testosterone compounds. Unsurprisingly, women aged 50–59 years have been the primary beneficiaries of testosterone prescriptions [102]. The reasons for prescribing included not only sexual dysfunction, but also gender dysphoria[103], osteoporosis, and depression[104].[105]

Finally, as noted previously, women may have a particular need for testosterone in treatment of anorexia nervosa ("AN") which afflicts women at a far greater rate than men[106], and is often accompanied by depression. Treatment with transdermal testosterone demonstrated antidepressant effects in a three-week study of women with AN and depression[107]. As this is a potential use for testosterone therapy, but falls under the heading of mental health, it is unclear under the new rules whether the exemption on two-way audio-visual communication is permissible. In addition, there are other medical specialties outside of mental health disorders that rely more heavily on audio without the need for video communication at all. The provider and patient should have the ability to make a uniform decision on the care being provided to the patient based on their individual needs.

Endocrine complications are common in anorexia nervosa (AN). Examples include absence of menstrual periods in women, low testosterone levels in men, and low thyroid hormone levels, all of which are considered adaptive to the state of undernutrition[108]. As this requires specialized treatment, now requiring in-person treatment from the prescribing physician, those afflicted by AN will face additional hardship when seeking treatment.

Examining physicians may not be trained in appropriate androgen therapies for men, but this is even more likely with regards to the emerging field of androgen use in women. Examining physicians would be less likely to provide a referral for this, due to this common lack of

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[98] Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? Fertil Steril 2001;76:456-460

[99] Judd HL, Judd GE, Lucas WE, Yen SS. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 1974;39:1020-1024

[100] Nathorst-Boos J, von Schoultz B. Psychological reactions and sexual life after hysterectomy with and without oophorectomy. Gynecol Obstet Invest 1992;34:97-101

[101] But note that conditions that upset the production of androgens can result in the same deleterious effects in males.

[102] Nathorst-Boos J, von Schoultz B. Psychological reactions and sexual life after hysterectomy with and without oophorectomy. Gynecol Obstet Invest 1992;34:97-101

[103] Discussed infra.

[104] Baillargeon, J., Urban, R. J., Raji, M. A., Westra, J. R., Williams, S. B., Lopez, D. S., & Kuo, Y. F. (2020). Testosterone Prescribing Among Women in the USA, 2002-2017. *Journal of general internal medicine*, *35*(6), 1891–1893.

[105] Davis, S. R., & Wahlin-Jacobsen, S. (2015). Testosterone in women--the clinical significance. *The lancet. Diabetes & endocrinology*, *3*(12), 980–992.

[106] Schorr, M., & Miller, K. K. (2017). The endocrine manifestations of anorexia nervosa: mechanisms and management. *Nature reviews. Endocrinology*, *13*(3), 174–186.

[107] Miller KK, Grieco KA, Klibanski A. Testosterone administration in women with anorexia nervosa. J Clin Endocrinol Metab. 2005;90(3):1428–1433. doi: 10.1210/jc.2004-1181.

[108] Haines M. S. (2023). Endocrine complications of anorexia nervosa. *Journal of eating disorders*, *11*(1), 24.

familiarity. This would require telehealth specialists to spend a considerable amount of time and resources to locate and secure partnerships with community providers in every zip code the in which the remote-prescribing physician is licensed.

VII. Pandemic Preparedness

Although the official Public Health Emergency as declared by Department of Health and Human Services is set to expire on 11 March 2023, the painful lessons taught by the COVID-19 virus should not be forgotten. In-person visits to a physician's officer carry with them the risk of acquiring a viral infection[109,110]. The recommended preventative to acquiring a viral infection through an in-person visit is to utilize telehealth[111]. This recommendation, obviously, has a success rate of 100%.

There is also a potential socio-economic component to telehealth. Telehealth often relies on the examining physician to make a referral to a specialist. Telehealth allows for this specialist, who would logically and practically be the prescribing physician as well, to be located anywhere in the United States. Many telehealth patients cannot afford to travel to a specialist across the country. Those of lower economic status often cannot afford to lose hourly wages by taking time out of the workday to visit a second doctor within 30 days.

The risk is amplified yet again for lower income households who, more frequently, have multiple generations living together. From an epidemiological standpoint, risk for viral pathogens is often greatly increased when factoring age and exposure.

The PHA declared in response to the coronavirus pandemic is set to officially end on 11 March 2023. But the tragic lessons of that crisis have taught us without question that practical safeguards against the spread of viral contagion can (and should) be maintained whenever possible. A single doctor's visit is preferable to multiple visits, especially when the second visit is a creature of statute, and not a medical necessity supported by current clinical guidelines. Decisions as to the time and manner of physician visits ought to be decided upon by the doctor and the patient, within the strictures of the law, but also with the realization that the newly proposed statutory requirements should not be allowed to displace medical decisions tailored to providing the most appropriate standard of care.

VII. Final Suggestions

Data has conclusively demonstrated that telehealth serves to produce a health care system that is more efficient, better coordinated, convenient, and affordable for all. It helps to address health concerns for vulnerable populations with existing barriers to care such as income levels and access disparities. It does so through removing location and transportation barriers, unnecessary time out of work, potential childcare expenses, which may be consumed by each visit. The

[109] Avoiding infection: What to do at the doctor's office. (2008). *Paediatrics & child health, 13*(5), 420–437. https://doi.org/10.1093/pch/13.5.420

[110]https://twin-cities.umn.edu/news-events/new-study-shows-patients-visiting-their-doctor-after-flu-patient-are-more-likely-get

[111]https://www.scripps.org/news_items/4790-how-to-avoid-getting-sick-at-the-doctor-s-office

evidence shows high-quality outcomes, satisfaction, and success rates (a patient satisfaction rate of 95%).[112]

The limited supply of medication will place considerable strain on both the administrative and medical staff within practices to provide a limited prescription, only to provide subsequent prescription within a couple of weeks once the additional requirements are met. This is particularly inappropriate for testosterone, because of the overwhelmingly long-term nature of testosterone treatment protocols. It would be exceedingly rare for a protocol to not be long-term, with many extending for a lifetime (TRT, HRT, and gender affirmation therapy) or in the alternative lasting for at least several years (cachexia and wasting diseases).

For prescriptions of testosterone and other androgens, the mandated second visit within 30 days is overly burdensome and contradicts the underlying core rationale of telehealth—that increased accessibility through technology will reduce barriers to effective care. Data produced within 30 days of beginning hormone therapy will be negligible at best, while greatly inconveniencing the patient with a visit that could have been a phone call, video conference, or lab work. Requiring a physician appointment within 30 days conflicts with clinical guidelines established by multiple medical associations including the American Urological Association (AUA), Endocrine Society (ES), and International Society of Sexual Medicine (ISSM). The follow-up requirements for testosterone replacement therapies range from 3 months or 6 months to once per year on maintenance therapy[113,114].

A more reasonable timeframe would be 90 to 180 days, at which point the patient and prescribing physician would be able to assess the efficacy (or lack thereof) of the prescription and protocol and have cognizable data from which to make an informed decision to either continue or modify as warranted. Another option would be to opt for bloodwork at 45 days, when long acting testosterone esters would reach steady state blood plasma levels. This could be done in lieu of the proposed in-person visit with the prescribing physician, as it would provide the necessary data point for adjustment of dose or compound.

The patient should always have the option to opt-in or opt-out of video communication. Telehealth provides an opportunity the underserved to access medical care from anywhere. This would be adversely impacted by any rule requiring the doctor to have inappropriate access to view not only the patient, but the patient's home or place of work. This would be an unacceptable barrier to care for some patients, who may not feel comfortable "inviting" (or allowing) their physician into their living or occupational situation, for a myriad of reasons. The majority of telehealth services are done from the comfort of the patient's home, and it is an unwarranted invasion of privacy to mandate that the physician should have the obligation to view the patient in this setting. In addition, with regards to the geriatric population[115], or other populations without the technical sophistication or means to access video communication

[112] VanderWerf, M., Bernard, J., Barta, D. T., Berg, J., Collins, T., Dowdy, M., Feiler, K., Moore, D. L., Sifri, C., Spargo, G., Taylor, C. W., Towle, C. B., & Wibberly, K. H. (2022). Pandemic Action Plan Policy and Regulatory Summary Telehealth Policy and Regulatory Considerations During a Pandemic. *Telehealth journal and e-health : the official journal of the American Telehealth Association*, *28*(4), 457–466.

[113] Jethro C.C. Kwong, BMSc, Yonah Krakowsky, MD, Ethan Grober, MD, Testosterone Deficiency: A Review and Comparison of Current Guidelines, *The Journal of Sexual Medicine*, Volume 16, Issue 6, June 2019, Pages 812–820

[114] Pelzman DL, Hwang K. Testosterone therapy: where do the latest guidelines agree and differ? Current Opinion inEndocrinology, Diabetes, and Obesity. 2020 Dec;27(6):397-403.

[115] A sizable component of those requiring hormone replacement therapy

devices, there should exist the possibility to make a decision for utilization of exclusively audio communication.

In circumstances where internet issues arise or the video communication is not feasible, the provider and patient should have the right to default to a phone call to complete the consultation and not withhold care due to technical difficulties. This would, of course, be predicated on the establishment of the doctor-patient relationship and primarily to ensure that the level of care remained in-tact and not sacrificed in any way. Additional record keeping requirements include the time of the visit to be noted along with the date. This is an unnecessary requirement and it is unclear as to whether and why it would provide useful information.

The new rules proposed under DEA-407 are unnecessary to prevent diversion. They are unwarranted to increase patient safety, and they will impose burdensome and dangerous protocols that will decrease patient access to care and limit the number of doctors available and allowed to provide that care. They should be reconsidered and revised in accordance with the available science, facts, and best practices.