

## The Benefits of Subcutaneous Delivery of Pelletized Drug Formulations Using a Novel Access and Insertion Device: *Reduction of Tissue Damage and Minimization of Extrusion Lead to Increased Compliance*

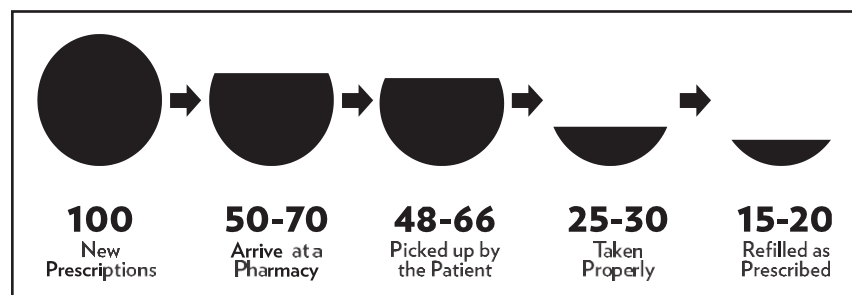
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### **Background**

The American health care system has numerous issues that contribute to the skyrocketing costs of health insurance and prescription medications, with one of the principal problems stemming from the culture of reactive sick care and polypharmacy. Reactive health care is certainly important if you have already sustained an injury or already are ill – but does nothing to keep the body healthy in the first place. Polypharmacy is a byproduct of reactive health care, when a patient is prescribed multiple medications from multiple providers for multiple disease states and symptoms – but none of which are preventative in nature or address the root cause of the condition. This cascading buildup of medications can and does spiral into the biggest issue in medicine today: patient noncompliance.

Patient noncompliance, when patients don't take one or more of their medications as prescribed, results in 125,000 preventable deaths each year. Reasons for patient noncompliance include forgetfulness, misunderstanding, fear or worry, complex medication schedules, adverse drug reactions, and cost. Noncompliance currently costs the healthcare system \$524 billion annually in preventable costs, a figure that is expected to approach \$1 trillion by the end of the decade. Only 25-30% of new prescriptions are actually taken properly (**Figure 1**),<sup>1</sup> and an astonishing 25% of all hospital admissions are a result of medication non-compliance.<sup>2</sup> Ninety five percent of payors indicate noncompliance is a “very serious” issue for their companies and seventy three of payors have spent money in the last year trying to fix this problem. While noncompliance is frequently the result of patients intentionally or unintentionally not taking their medications as prescribed, some fault also lies in the polypharmacy culture itself and the nature of prescription modalities.

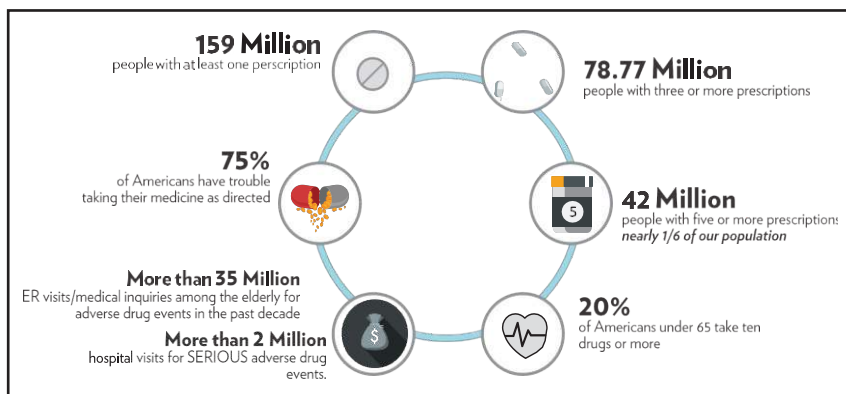
With just under half of the US population regularly taking at least one prescription drug and nearly 20% of the elderly population taking 10 drugs or more, a patient's risk of suffering a serious side effect is significant, and the opportunity for noncompliance is rampant (**Figure 2**).<sup>3-5</sup>



**Figure 1.** The Problem of Patient Noncompliance.<sup>1</sup>

The answer to this scattershot approach to multiple medications and the resulting noncompliance is paradigm shift towards true preventative health care. In other words, instituting a therapy that changes the trajectory of a disease state by delaying or reversing a total body breakdown. Various treatment modalities and routes of administration can be considered, but none perform with the certainty in compliance like subcutaneously implanted, sustained release medications.

Hormone therapy is a prime example of an indication where noncompliance and reactive sick care are prevalent. Like maintaining oil in the engine of a well-running car, the sustained delivery of bioidentical testosterone or estrogen has been shown to maintain the body in a healthy state. Just one hormone, consistently delivered at the right dose, can address depression, fatigue, anxiety,

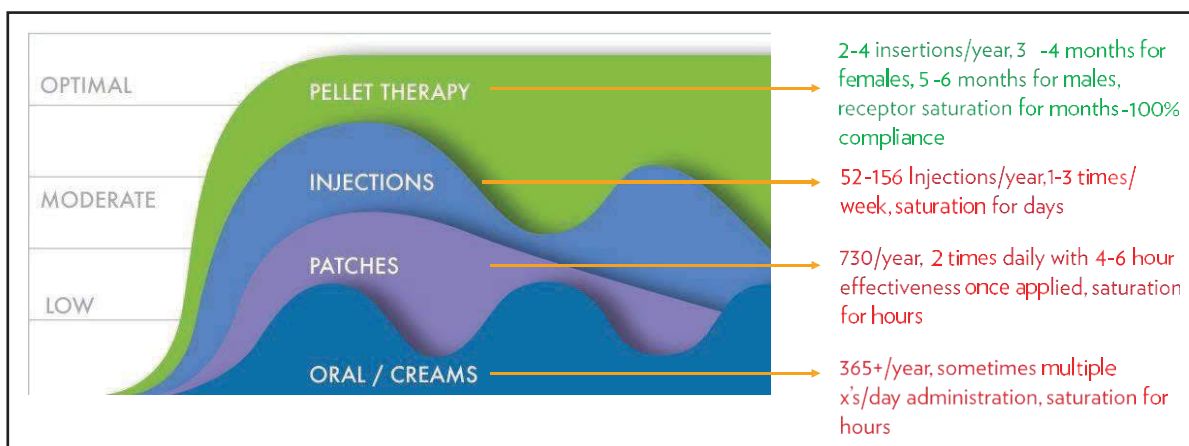


**Figure 2.** Polypharmacy and Noncompliance.<sup>3-5</sup>

neurocognitive decline, osteoporosis, heart function, weight gain, erectile dysfunction, vaginal dryness, hot flashes, night sweats, and chronic pain. With the standard ‘reactive sick care’ approach, a patient with several of these symptoms would be prescribed different single medications for each one, each with its own unintended side effects, potential contraindications, and intentional or unintentional noncompliance.

Options for hormone therapy include injections, creams, patches, pills, and pellets. All of these modalities except for pellets put the patient on some kind of a blood level roller coaster that does not provide the patient with the desired relief. Pellet therapy involves using a handheld trocar instrument to penetrate the skin and access a subcutaneous region of the body to implant a distinct ‘pelletized’ formulation of a medication that releases the active ingredients of the drug over time in a sustained manner.<sup>6</sup>

Patients prefer pellet-based hormone therapy for three main reasons. First, they get much better short-term relief of their symptoms. Pellet therapy is the only modality that delivers medications through zero-order kinetics, achieving optimal range for months at a time, as opposed to only hours or days from the others (Figure 3). Second, it is preventative in nature. Pellet therapy optimizes the hypothalamic – pituitary – testicular axis, so the patient doesn’t spiral into other disease states. Lastly, it is a convenient “set it and forget it” modality, where patients don’t have to remember to take it, all but eliminating noncompliance issues.



**Figure 3.** Drug Delivery Profiles and Patient Compliance of various administration modalities.

However, traditional pellet therapy is also not without complications. The predominant surgical tool used for pellet insertion has a sharp or beveled edge. It was first developed in 1939, and is essentially the same design today. This sharp design has the unfortunate effect of permanently damaging the subcutaneous

septal fibers, microvasculature, and adipose tissue. This created two issues. First, in order for medication to be absorbed properly it needs a healthy vasculature – and the sharp instrument was disrupting that critical blood flow. Second, the damaged tissues were physically weaker and had more ‘failure points’, where it was much easier for a pellet to dislodge and extrude out from its implantation site. These extrusions were painful to the patient, and resulted in medication noncompliance. A published analysis of patients receiving traditional pellet insertion therapy documented an extrusion rate of 11-12%<sup>7</sup> - far too high of a complication rate to be broadly accepted by the general public in an effort to minimize noncompliance.

All trocars (G.I., laparoscopic, and orthopedic) have transitioned to a blunt design. Until the invention of the atraumatic trocar there has not been an alternative to this traditional method of pellet insertion and its resulting complications (**Figure 4**). With over 1.65 million annual insertions of hormone pellet insertion currently with the traditional sharp trocar, there is a significant opportunity for the blunt atraumatic trocar in just this narrow hormone therapy market.



**Figure 4.** Renderings of the novel blunt-tipped insertion device, and an image of the surgical convenience kit used for pellet implantation procedures.

### **Clinical Assessment: Hormone Therapy**

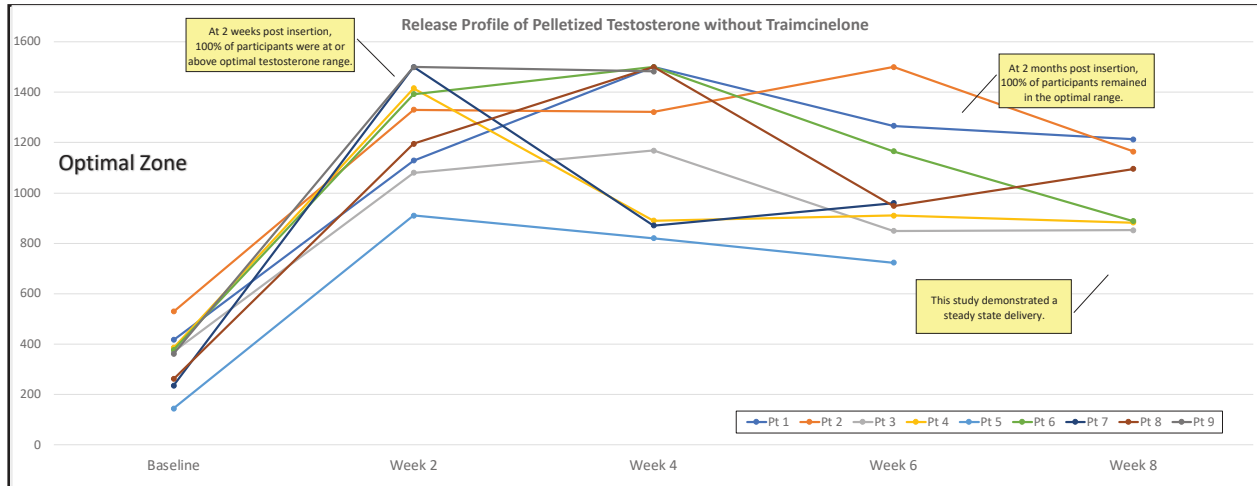
An age-related decline in testosterone levels in men, likely due to a combination of primary (testicular) and secondary (hypothalamic) mechanisms,<sup>8</sup> is just one indication in which long-term testosterone treatment is prescribed. Clinically, women are prescribed testosterone for fatigue, libido, depression, and osteoporosis. Approximately 43% of women in the United States between the ages of 18 and 59 experience sexual dysfunction. Four million annual prescriptions are written off-label for hypoactive sexual desire. Of the estimated 10 million Americans with osteoporosis, about eight million or 80% are women. These are just some of the hormone therapy opportunities that safe and effective pellet therapy can address.

### ***Drug Delivery Profile***

Two principal questions can be posed with respect to the effective dose of testosterone for hormone therapy. First is the question of release profile. Prior studies of pelletized testosterone have demonstrated an optimal effective serum total testosterone level of 400-1100 ng/dL.<sup>9</sup> Serum testosterone levels were assessed in a series of nine TheraPelLET, LLC patients who voluntarily received pelletized testosterone implanted with the blunt trocar. Volunteers ranged from 35-65 years old with BMIs ranging from 14-30%. All participants had normal PSA ranges, were prostate symptom free, off blood thinners, with normal hemoglobin and hematocrit levels. Patients were followed with bi-weekly blood draws, with lab testing performed by

LabCorp, Inc. As shown in **Figure 5**, at 2 weeks post-insertion 100% of participants were at or above optimal testosterone range. At 2 months post-insertion, all of the participants remained in the optimal range.

This maintenance of a sustained steady state delivery demonstrates the potential effectiveness of the combination of pelletized testosterone inserted with the blunt-tipped trocar.



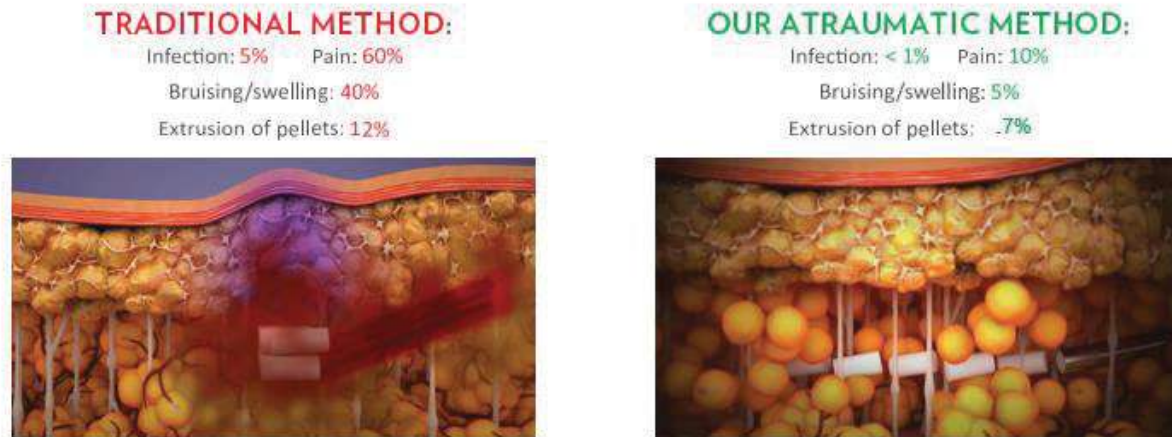
**Figure 5.** Testosterone release profile (without triamcinolone) on 9 patients after implantation using the atraumatic blunt-tipped insertion device. Sustained steady-state delivery was observed.

The second question relates to the adjunct use of triamcinolone. This ancillary drug has demonstrated benefits related to the pain reduction, release kinetics and absorption effectiveness of pelletized testosterone therapy when inserted with a traditional sharp trocar. However, its benefits when utilized in conjunction with the newly-developed blunt-tipped trocar insertion technique are negligible at best (Virden, unpublished data). In fact, the combination appears less effective than testosterone alone. This is likely due to the lack of trauma and tissue damage at the site as a result of the blunt-tipped trocar. As triamcinolone acts to reduce cell signaling, in a traumatized environment this serves to appropriately calm down the signaling and allow appropriate absorption of drug into the tissue. In an atraumatic environment however, the cellular signaling is overly calmed by triamcinolone, leading to minimal drug absorption, and therefore lower effectiveness. As a result, subsequent clinical efforts focused on pelletized testosterone without triamcinolone, targeting the delivery profile reported above.

### ***Clinical Safety Series***

Using the newly-developed proprietary blunt tip access device, 3905 consecutive pellet insertions over the 2021 calendar year for hormone therapy at TheraPellet, LLC were followed to evaluate patient complaints and pellet extrusions. Volunteers again ranged from 35-65 years old, both with and without prior pellet therapy. A total of 13,798 pellets were implanted as part of this large series.

**Only 28 extrusions were observed, a rate of 0.7% per insertion.** This compares highly favorably to the historical extrusion rate of 12% per insertion.<sup>7</sup> Total complaints, received at a rate of 2.0% per insertion, were also much lower than historical data. It is truly the revolutionary blunt tip technology advancement that greatly decreases the rate of extrusions, and as a result makes solving this patient compliance issue via pellet therapy possible (**Figure 6**).



**Figure 6.** Comparison of complication rates using the atraumatic blunt-tipped insertion device with traditional pellet insertion using a sharp tissue-damaging trocar.

## Summary

The use of a novel, atraumatic insertion device has been shown to enable effective, sustained delivery of testosterone (without triamcinolone) in an initial clinical assessment, and also greatly reduce pain, extrusion rates, and other complications in a large case series on patients receiving pellet-based hormone therapy.

This new gold standard technique using the blunt-tipped trocar enables the potential utility and acceptance of pellet therapy by the broader medical community and the general population. As a result, with a now-acceptable extrusion rate, there is a massive market opportunity to expand this therapy beyond testosterone and estrogen other drug markets to solve the biggest issue we face in medicine today: patient non-compliance.

## References

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