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Potential next-generation medications for self-administered platforms

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A B S T R A C T

The Coronavirus Disease (COVID-19) pandemic has reshaped clinical chronic disease management. Patients reduced the number of physical clinic visits for regular follow-up care because of the pandemic. However, in developing countries, the scattered healthcare system hindered accessibility to clinical consultation, and poorly controlled chronic diseases resulted in numerous complications. Furthermore, the longer patients suffered from the chronic disease being treated, the more physical and psychological stress they experienced. "Diabetes Burnout," as an example, is a term to describe the phenomenon of psychological reluctance in long-term glycemic control. A comprehensive, patient-centered, and automatic drug administration and delivery model may reduce patient stress and increase compliance. Potential next-generation medication platforms, consisting of internal regulation and external interaction, may conduct autonomous dose adjustment and continuous selfmonitoring with the assistance of artificial intelligence, telemedicine, and wireless technologies. Internal regulation forms a closed-loop system in which drug administration is optimized in an implanted drug-releasing device according to a patient's physiopathological response. The other feature, external interaction, creates an ecosystem among patients, healthcare providers, and pharmaceutical researchers to monitor and adjust post-market therapeutic efficacy and safety. These platforms may provide a solution for self-medication and self-care for a wide variety of patients but may be life-changing for patients who live in developing countries where the healthcare system is scattered, as they could effectively remove healthcare barriers. As the technology matures, these self-administrated platforms may become more available and increasingly affordable, offering considerable impact to health and wellness efforts worldwide.

1. Introduction

The Coronavirus Disease (COVID-19) pandemic has reshaped clinical chronic disease management models. More clinicians adapted to telemedicine to deliver care through virtual healthcare and digital technologies, and patients reduced the number of physical clinic visits for regular, follow-up care. Patients did not avail themselves of telemedicine opportunities for follow-up care. In this manner, the pandemic thus interfered with regular, follow-up healthcare and actually weakened chronic disease management.

Chronic diseases, such as diabetes or cardiovascular disease, put a tremendous and increasing burden on both individuals and healthcare systems worldwide. These chronic diseases have contributed to the largest share of deaths and disabilities and account for huge healthcare expenditures [1]. In the United States, a developed country, these expenditures gradually increase, accounting for 90% of all annual healthcare spending in the US [2]. In developing countries, on the other hand, the scattered healthcare system hindered accessibility to clinical consultation, and poorly controlled chronic diseases resulted in numerous complications [3].

Self-medication might be the pivotal approach solution for managing these conditions. Self-medication is defined by the World Health Organization as follows: "self-medication involves the use of medicinal products by the consumer to treat self-diagnosed disorders or symptoms, or the intermittent or continued use of medication prescribed by a physician for chronic or recurrent diseases or symptoms [4]." The essential challenge before us then, is to build long-term, reliable, self-administrated, and convenient drug delivery strategies for chronic diseases management.

2. Evolution of drug delivery science

In terms of drug-release control, there have been three developmental generations: 1) fundamentally controlled release; 2) "smart" delivery; and, 3) modulated delivery systems. The controlled-release generation began from a 12-hour delivery formula for dextroamphetamine (Dexedrine) introduced by Smith Kline & French in 1952 [5]. With the understanding of various drug release mechanisms, like dissolution, diffusion, osmosis, and ion exchange, numerous twice-a-day or once-a-day oral delivery systems were introduced [5]. In the second-generation, drug delivery science focused on "smart" delivery systems. Zero-order drug delivery systems were introduced to achieve a constant

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rate of dose releasing, thereby maintaining drug concentrations within the therapeutic window for an extended period. Following this, "smart" polymer or hydrogel technology was introduced, which allowed drugs to be delivered in an inactivated form and subsequently activated at the targeted area by local environmental changes such as pH, temperature, etc. [5]

With the advance of bionanotechnology, drug delivery scientists launched several innovative drug delivery systems to satisfy various clinical situations [5]: 1) the pulsatile drug delivery systems (PDDS) [6]; 2) dynamic nanoassembly-based drug delivery systems (DNDDS) [7]; and, 3) long-acting drug delivery systems (LADDS) [8].

The pulsatile drug delivery systems (PDDS) permitted drugs to be released at the right time. Human beings exhibit circadian rhythms, and these pulsatile drug delivery strategies were expected to coordinate with pathophysiological rhythms to maximize the therapeutic effect while minimizing side effects. Pulsatile drug delivery strategies might be beneficial for managing chronic diseases like hormonal disorders or some neurological disorders. The dynamic nanoassembly-based drug delivery system (DNDDS), on the other hand, is focused on maximizing therapeutic effect at targeted sites. Drugs are administered in inactivated forms and activated by specific pathophysiological or physiological microenvironments in the designated area to minimize side effects [7]. Long-acting drug delivery systems (LADDS) provide a more extended period of therapeutic effects from a single dosage by optimizing the drug's pharmacokinetics and pharmacodynamic activity. The sustained drug-releasing duration ameliorates patient compliance with less frequent dosing, enhances comfort by eliminating repeated injections, and provides localized, site-specific drug delivery [8].

3. Chronic disease and self-medication

Although current drug delivery strategies provide more precise pharmaceutical administration at the right time and the right place, several clinical difficulties impede the control of chronic diseases: poor medication compliance, inadequate drug dosage, or reluctance to medication control due to side effects, etc. The longer patients suffered from the disease being treated, the more physical and psychological stress they experienced. These burdens further decrease long-term patient compliance with chronic illness control and increase cognitive stress and mental sickness. "Diabetes Burnout," for example, is a term to describe the phenomenon of psychological reluctance in long-term glycemic control [9]. A comprehensive, patient-centered, and automatic drug administration and delivery model may reduce patient stress and increase compliance.

The MiniMed Paradigm REAL-Time System (Medtronic Diabetes, Northridge, CA) was launched in 2006. This device was an insulin delivery device integrated with real-time continuous glucose monitoring (CGM). With a closed-loop insulin delivery system, insulin was administrated according to the detected serum glucose level [10]. The Medtronic MiniMed had allowed more diabetic patients to gain a higher degree of treatment satisfaction and compliance. These innovative approaches to self-administrated implanted devices might inspire us to establish the next generation of drug-delivery platforms.

4. Potential next-generation self-administered medications platforms

Potential next-generation medication platforms will consist of two primary features—internal regulation and external interaction. Internal regulation forms a closed-loop system in which drug administration is optimized in an implanted drug-releasing device according to a patient's physiopathological response. The other feature, external interaction, creates an ecosystem among patients, healthcare providers, and pharmaceutical researchers to monitor and adjust post-market therapeutic efficacy and safety.

I. Internal regulation of drug administration–a closed-loop systems

As far back as 1892, the Canadian physician, Sir William Osler noted, "If it were not for the great variability among individuals, medicine might as well be a science, not an art." While clinical physicians and drug scientists developed and provided medicine based on the evidence of objective randomized clinical trials and applied to "statistically average patients" decades ago, more scientists have begun to recognize the influence of variable responses on therapeutic results for different individuals [11]. These diverse therapeutic responses may also be attributable to drug properties (narrow therapeutic range, pharmacokinetic/pharmacodynamic variability), disease characteristics and status, and patient-specific factors (e.g., organ function, gene variants, or ethnics). Clinically it is crucial but challenging to administrate dosages appropriate for specific disease status to maximize therapeutic effect and minimize side effects. Glycemic control, as an example, is affected by a patient's lifestyle, health, and even fasting status. Daily adjustments in insulin supplementation are challenging, but dosages were traditionally established following simple rules based on empiricism or experienced clinicians' suggestions. Preset and advised drug administration frequently results in more adverse events if a healthcare system is inaccessible [3].

Self-regulated drug delivery devices with closed-loop systems are designed to achieve autonomous delivery of therapeutics and improve patient compliance. A micro/nano sensor detects subtle in vivo pathophysiological change of targeted tissue/markers and monitors in vivo drug concentrations, generating feedback systems to modify drug release until the concentration achieves the therapeutic level [12].

The closed-loop administration systems consist of biomarker detectors, data analyzers, and drug-releasing regulators, as shown in Fig. 1.

a. A biomarker
   - ◆ A biomarker is defined as a measurable biochemical substance that is used to recognize the presence and severity of a disease, or a response to therapeutic interventions [13]. This biomarker may be a form of a biomolecule or a biological structure, such as RNA, protein, or peptide, etc. Like glucose versus insulin, the serum glucose level is a crucial element in observing the response to insulin therapy.

b. A biosensor and transducer
   - ◆ Biosensors can be broadly defined as devices used to detect a biological analyte's presence or concentration and produce recognizable signals with a transducer. Recently, nanotechnology leveraging the electrochemical characteristics of carbon or conductive polymers has been proposed as desirable methodology for developing biomarker detectors and transducers. With transducers, electrical or optical signals can be transduced and captured [14]. These biosensors can be integrated into theranostic devices for real-time monitoring.

c. Machine learning and artificial intelligence
   - ◆ Precision dosing means optimizing an individualized drug-delivered dosage to achieve a therapeutic effect without causing drug toxicity. Machine learning offers a promising way to reform medical diagnosis and therapy by providing accurate and individualized analysis and forecasts based on a vast amount of patient data [12]. With continuous monitoring, even a small number of patients can generate a vast amount of data for analysis, which can further facilitate machine learning [3].
   - ◆ Given the advances in nanobiotechnology, more biocompatible nanodevices might be introduced in the future. These biocompatible nanodevices combined with computer chips can further expedite the application of artificial intelligence in drug-delivery systems.

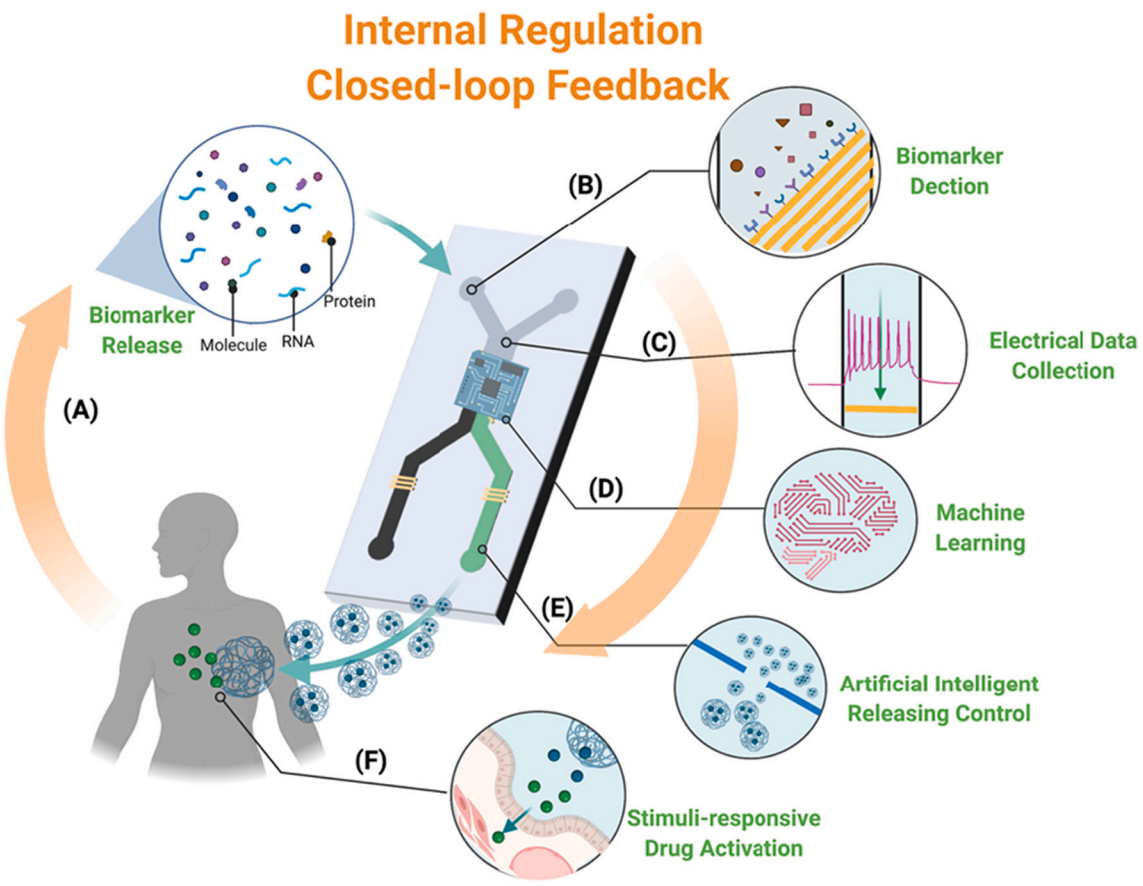

Fig. 1. Internal regulation and closed-loop feedback system. The closed-loop administration systems consist of biomarker detectors, data analyzers, and drug-releasing regulators: (A) Biomarker release: A biomarker is defined as a measurable biochemical substance that is used to recognize the presence and severity of a disease, or a response to therapeutic interventions. This biomarker may be a form of a biomolecule or a biological structure, such as RNA, protein, or peptide, etc. (B) Biosensors can be broadly defined as devices used to detect the presence or concentration of biomarkers. (C) Transducer produce recognizable electrical or optical signals. (D) Machine learning is established and generated by continuous bioelectrical data analysis. (E) Drug release is controlled by the assistance of artificial intelligence. (F) With targeted stimuli-responsive drug delivery integration, the drug is designed to be primarily released and activated at the targeted area. Figure is created with BioRender.com.

d. The integration of targeted stimuli-responsive drug delivery systems [15]
   - ◆ Compared to traditional monotonic drug-release manners, newer drug carriers can precisely control the release time and quantity of drugs introduced into a patient's body by programmed and on-demand means [15].

e. With stimuli-responsive designs, drugs are produced and administered in inactivated forms and then activated by specific pathophysiological or physiological microenvironments at the target site, which minimizes side effects [7].

II. External interaction forms an ecosystem

As the COVID-19 pandemic has spread globally since 2020, social distance and travel restrictions have made more people "stay home". Telemedicine, no doubt, is an emerging and evolving technology to accommodate medical needs via at-home screening, diagnosis, and monitoring. In 2019, Nicola Di Trani et al. introduced a remote-control drug-delivery device, controlling the rate of drug administration via Bluetooth [16]. This technology not only allows patients to control drug release externally but inspires a novel means of data transmission – wireless data communication between the implant and areas outside the body. With internet and cloud synchronization of the transmittable dataset, health providers can also offer professional advice based on the collected information [17]. Thanks to the improved infrastructure of the fourth industrial revolution (Industry 4.0) supported by 5G and the Internet of Things (IoT), a cloud-based drug-delivery ecosystem can be established by leveraging real-time analytics and machine learning [17].

This ecosystem consists of three parts: patients, healthcare providers, and pharmaceutical researchers, as shown in Fig. 2.

a. Patients
   - ◆ Within vivo implants and remote-control systems, patients can also adjust their drug dosage according to subjective measures. In pain control, for example, clinicians face the challenge of inadequate chronic pain control due to a lack of monitorable biomarkers. With a preset limitation of maximal analgesic dosage and releasing intervals, patients gain more satisfaction and quality of life via extracorporeal patient-controlled analgesics devices [18].
   - ◆ Meanwhile, as devices are put in place and used more and more frequently, more data are generated and collected [3]. This information can be de-identified and transmitted through the internet or cloud systems to the healthcare providers or pharmaceutical researchers.

b. Healthcare providers
   - ◆ It is crucial but challenging for clinicians to employ clinical consultation alone to prescribe dosages appropriate to specific disease status in order to maximize therapeutic effect and minimize side effects.
   - ◆ Furthermore, implanted drug-delivery devices provide continuous information regarding a patient's

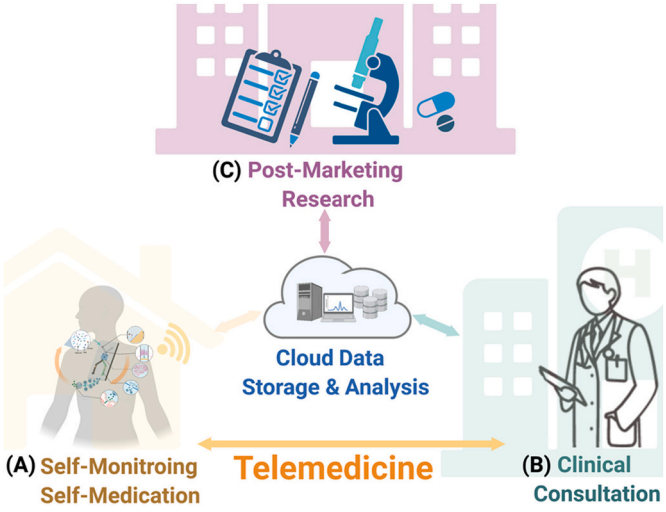

Fig. 2. External interaction forms an ecosystem. This ecosystem consists of three parts–patients, healthcare providers, and pharmaceutical researchers: (A) Patients. Integrating in vivo implants and remote-control systems (like Bluetooth), allows patients to adjust their drug dosage according subjective measures. Wireless technologies also permit patients to transmit their data from the implant to the internet or cloud systems anonymously. (B) Healthcare providers. Combined with the vital sign monitoring, information from other wearable devices, the data from implanted drug-delivery devices, and patients' subjective responses, clinicians can provide proper medical advice via telemedicine. (C) Pharmaceutical researchers. Given the wireless transmission and the anonymous big data analysis combined with machine learning, post-marketing drug efficacy and pharmacovigilance systems can be established. Figure is created with BioRender.com.

physiopathological response to administrated medication. Combined with vital sign monitoring, information from other wearable devices, the data from implanted drug-delivery devices, and patients' subjective responses, clinicians may provide more appropriate advice through a virtual visit.

III. Pharmaceutical researchers
   a. Because diverse therapeutic responses may be attributable to various factors, post-marketing drug response and safety surveillance are essential. In contrast to data from randomized controlled trials, real-world data provides more extended observational periods and more prominent, heterogeneous study populations reflecting more precise medication response because some individuals might not be recruited in trials.
   b. With the assistance of anonymous data analysis, machine learning, and wireless transmission, post-marketing drug safety and efficacy can be evaluated more precisely. Furthermore, when combined with reported adverse events, pharmacovigilance systems can also be established to avoid drug toxicity and interactions [19].

5. Conclusion and outlook

Self-care is a manner or behavior practiced by people to maintain wellness and avoid diseases. It comprises not only health-promotion practices, but may include technological disease prevention and control efforts, self-medication methodology, and in -person or telemedicine-based clinical guidance.

Currently, more than half of the world lack access to essential health services, and the World Health Organization has urged the need for developing self-care and self-medication methodologies. Meanwhile, The World Health Organization has encouraged the use of mobile wireless technologies for public health (mHealth) as a means of revolutionizing public health services and urged its Member States to achieve universal health coverage by utilizing information and communication technologies for health (eHealth) [20]. Ensuring healthy lives and promoting well-being for all ages has been addressed as a Goal for Sustainable Development [21].

The potential next-generation self-administered medications platforms may conduct autonomous dose adjustment and continuous self-monitoring with the assistance of artificial intelligence, telemedicine, and wireless technologies. These platforms may provide a solution for self-medication and self-care for a wide variety of patients, but may be especially life-changing for patients who live in developing countries where the healthcare system is scattered, as they could effectively remove healthcare barriers. As the technology matures, these self-administrated platforms may become more available and increasingly affordable, offering considerable impact to health and wellness efforts worldwide.

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