Selected Summaries

Treatment adherence to tuberculosis: What works

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SUMMARY

This open-label, prospective, randomized controlled trial was done in San Diego (SD) and Orange County (OC) in the USA. Wirelessly observed therapy (WOT) is a novel patient self-management system consisting of an edible ingestion sensor (IS), external wearable patch and paired mobile device that can detect and digitally record ingestion of medication. The study was done in two stages with an intention-to-treat analysis. Stage 1 evaluated the accuracy of WOT and stage 2 compared WOT and directly observed treatment (DOT). The primary end-points of the trials were: (i) positive detection accuracy (PDA) of WOT (defined as the percentage of IS-Rifamate ingestions detected by WOT when administered under direct observation); and (ii) the proportion of prescribed doses confirmed by WOT in comparison to DOT. Randomization was generated centrally via an algorithm residing within the study database. Block randomization into arms followed a 2:1 allocation, stratifying by study site (SD county and OC), was done. Study participants were adults with tuberculosis (TB) in the continuation phase of treatment who were smear-negative and taking isoniazid and rifampicin, with no evidence of drug-resistant TB. Participants with the ability to use a mobile device, understand written or verbal information regarding WOT and be willing to wear a patch were included. Patients who were pregnant or hypersensitive to skin adhesions were excluded from the study. In stage 1, 77 participants were enrolled in the study for PDA (12 persons enrolled for bioequivalence left after stage 1). In stage 2, 61 participants were randomized 2:1 to the WOT and DOT arms. Stage 1 was 2–3 weeks' duration and included training on WOT use and patch changes. In stage 2 initially, participants in both arms after randomization into WOT arm and DOT arm were to be followed for 16 weeks; however, because participants using WOT did not want to go back onto DOT, they were allowed to continue WOT until the end of the participants' treatment course. The PDA of WOT was 99.3% (95% CI 98.1–100), participants received DOT and WOT simultaneously for 2–3 weeks to allow calculation of WOT PDA and the 95% CI was estimated using the bootstrap method with 10 000 samples. Intent-to-treat analysis within the trial showed WOT confirmed 93% *v*. 63% DOT ($p<0.001$) of daily doses prescribed. Secondary analysis removing all non-working days (weekends and public holidays) and held doses from each arm showed WOT confirmed 95.6% *v*. 92.7% ($p=0.31$); WOT was non-inferior to DOT (difference 2.8% [95% CI: –1.8%–9.1%]). All the participants preferred using WOT. There was no significant difference in the rate of adverse events between the WOT and DOT arms. All participants stated they would prefer to continue to use WOT and not DOT after stage 1. The findings of this study suggest that WOT offers advantages over DOT for confirmation of adherence to TB treatment.

COMMENT

Mycobacterium tuberculosis complex infects a quarter of the world's population. In 2017, active TB was present in 10 million people, causing death in 1.4 million.[1] In the past decade, major advances have taken place in TB, both in diagnostics and therapy.[2] Multiple lines of evidence indicate the need for improved support to adhere to treatment. Poor adherence to treatment is associated with delays in sputum conversion.[3] In high-burden areas, it can be difficult to distinguish between relapse and reinfection. Irregular adherence to treatment is also associated with relapse.[4] Poor adherence has also been identified as a major factor in the emergence of multidrug-resistant (MDR) TB. DOT is currently the method recommended to ensure treatment adherence and reporting, and is available on 5 of 7 days of therapy at best. Digital health interventions such as short messaging service (SMS) and electronic pillboxes have also shown improvement in successful treatment but have not been compared to in-person DOT. DOT has been described as intrusive and disempowering for patients.[5] A novel sensor platform to monitor medication adherence to digitally capture daily ingestion of medication and analyse and support medication adherence in near real-time is needed. This system, termed WOT in the context of TB treatment adherence support, allows date and time stamping of ingestion. The system consists of an IS—approximately 1 mm^3 (1 mm × 1 mm × 0.45 mm)—coated with thin layers of commonly ingested excipients (that is, minerals and metals). A small adhesive-backed detector patch worn on the torso, and a paired mobile device is required. When ingested with a medication, the sensor readily separates from the carrier and communicates with the detector patch. The detector patch interprets the information as unique to the ingested sensor. Data are transmitted wirelessly, via Bluetooth technology, to a paired device such as a mobile phone, tablet or personal computer. All the data on the paired device are uploaded to a secured, centralized data storage location.[6] These data are available in near real-time to the patient and, with patient's permission, to healthcare personnel and other relevant persons, who can access these data from a secure web portal.

The technology, with its ability to transfer information over wireless and cellular networks, means that WOT-related follow-up can be essentially unlimited. DOT requires a large public health infrastructure in terms of personnel and offline reporting. WOT was safe, with side-effects limited to skin irritation associated with wearing the patch, and was easy to use. None of the participants in the trial wanted to be returned to DOT. A majority of the study population did not have advanced education or English as their first language. WOT utilizes a 'Bring Your Own Device' smartphone system and a newer, adhesive patch changed every 5–7 days with a single reusable detector hub. It is critical that WOT be tested in high-burden TB settings.

This trial includes the collection of data only during the

continuation phase of TB therapy, which is a limitation. Since the people were selected from the continuation phase, it is likely that they observed strict discipline. The fear of using sensors and wearing patches in illiterate people and the cost involved in using WOT is unclear when compared with DOT. Inability to use in unconnected areas and risk of leak of data stored in cloud storage are some areas of concern.

Implications for India

Missed doses were a major risk factor among defaulters in new smear-positive patients treated under short-course DOT in India.[7] Relapse rates are high within several TB programmes in high-burden countries such as India (15%–18%).[8] Irregular medication adherence was associated with relapse, and the degree of non-adherence was strongly associated with increasing risk of recurrence 18 months after completing treatment in programmatic care in India.[7] The ability of WOT to store digital treatment records, with the highest standards of encryption and constantly upgraded user-friendly software, could substantially support TB programmes in middle- and low-income settings such as India. However, under 'Bring Your Own Device' system, not everyone diseased with TB will be able to bring smartphones. While DOT remains the reference standard, it is resource-intensive, difficult to achieve—particularly over geographical distances—time-consuming and represents the largest single cost of TB treatment.[5] Furthermore, using WOT in a tribal population who have distinct dialects will be a challenge. While DOT can be manipulated and faked, WOT provides data on longitudinal patterns of ingestion of medication remotely. However, since the cost analysis part is unclear, it is too early to comment on replacing short-course DOT though the prospects look promising.

Conclusions

Cell phone-based communication technology has been adopted across the world where infrastructure development is lacking. WOT can provide near real-time actionable information, allowing patient-centred care to support adherence. This study suggests that WOT offers advantages over DOT for confirmation of adherence to treatment. WOT should be incorporated in implementation trials of oral MDR regimens in global settings.

Conflicts of interest. None declared

REFERENCES

1 WHO. *Global TB Report*. 2018. Available at *www.who.int/tb/publications/global_report/en/* (accessed on 28 Aug 2018).
2 Albert H, Nathavitharana RR, Isaacs C, Pai M, Denkinger CM, Boehme CC, *et al*. Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: What lessons have we learnt and how can we do better? *Eur Respir J* 2016;**48:**516–25.
3 Alipanah N, Jarlsberg L, Miller C, Linh NN, Falzon D, Jaramillo E, *et al***.** Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLoS Med* 2018;**15:**e1002595.
4 Cadosch D, Wiesch PA, Kouyos R, Bonhoeffer S. The role of adherence and retreatment in *de novo* emergence of MDR-TB. *PLoS Comput Biol* 2016;**12:**E1004749.
5 Weis SE, Foresman B, Matty KJ, Brown A, Blais FX, Burgess G, *et al*. Treatment costs of directly observed therapy and traditional therapy for *Mycobacterium tuberculosis*: A comparative analysis. *Int J Tuberc Lung Dis* 1999;**3:**976–84.
6 Hafezi H, Robertson TL, Moon GD, Au-Yeung KY, Zdeblick MJ, Savage GM. An ingestible sensor for measuring medication adherence. *IEEE Trans Biomed Eng* 2015;**62:**99–109.
7 Chandrasekaran V, Gopi PG, Santha T, Subramani R, Narayanan PR. Status of re-registered patients for tuberculosis treatment under DOTS programme. *Indian J Tuberc* 2007;**54:**12–16.
8 Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, *et al*. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. *Int J Tuberc Lung Dis* 2005;**9:**556-61.

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