REVIEW ARTICLE

Fentanyl for the Treatment of Tumor-Related Breakthrough Pain

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SUMMARY

Background: Breakthrough cancer pain (BTCP) is common among cancer patients and markedly lowers their quality of life. The treatment for BTCP episodes that is recommended in current guidelines involves extended-release formulations in combination with rapid-onset and short-acting opioids. In the past few years, several new preparations of fentanyl, an opioid with a very rapid onset, have been approved for this indication. Treating physicians need to be aware of the clinical differences between the newer fentanyl preparations and immediate-release opioids.

Methods: We searched the PubMed and Embase databases for randomized controlled trials (RCTs) of fentanyl for buccal, sublingual or intranasal administration in comparison with other opioids or a different fentanyl preparation for the treatment of BTCP.

Results: In 6 trials of buccal, sublingual or intranasal fentanyl versus oral immediate-release opioids for the treatment of BTCP episodes, the use of fentanyl was associated with significantly less intense pain. In particular, fentanyl more often lowered the intensity of pain by at least 33% (range between studies: 13% to 57%) or by at least 50% (range between studies: 9% to 38%) within 15 minutes. Please change to "versus" if you agree.] Dose titration should begin at the lowest dose. When one fentanyl preparation is exchanged for another, the effective dose will probably differ.

Conclusion: The newer fentanyl preparations extend the treatment options for BTCP. They relieve pain within a short time better than conventional, immediate-release oral opioids do and may therefore be very helpful for patients with suddenly arising, intense, and short-lasting BTCP episodes. Further comparative trials are urgently needed.

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Breakthrough cancer pain (BTCP) is a common symptom that markedly reduces cancer patients' quality of life (1). The point prevalence in cancer patients is over 50% (e1). Current treatment guidelines recommend the use of extended-release drugs in combination with rapid-onset and short-acting opioids (1–3).

For a long time, only immediate-release formulations such as morphine, oxycodone, or hydromorphone were available, which start to act within about half an hour. According to a current evidence-based treatment recommendation, these substances are indicated when BTCP is expected to occur, e.g., as triggered by movement, or when a single episode lasts for more than an hour (1).

For shorter episodes, fentanyl, a rapid-onset opioid, potentially offers an advantageous pharmacological profile; however, its enteral bioavailability is no more than moderate. Over the past few years, therefore, various oromucosal and nasal application forms have been developed.

While there has been little in the way of scientific studies of immediate-release oral opioids in BTCP, and their use is based mainly on clinical experience, in recent years several studies have reported on various fentanyl preparations (e2). A Cochrane review was also devoted to this topic in 2006, but unfortunately has not been updated since then (e3).

The aim of this review is to show, on the basis of comparative studies, the clinical differences between the various new fentanyl preparations and the immediate-release opioids used hitherto to treat BTCP.

Breakthrough pain

Breakthrough pain is defined as a sudden-onset, transient exacerbation of generally well-controlled background pain. It often occurs in the context of malignant disease. International surveys of patients consulting their doctors because of tumor pain showed an incidence of BTCP of 65% to 73% (e4, e5). A characteristic feature is abrupt onset, with the maximum often being reached within minutes (e6). The duration of episodes varies from seconds to hours, with a median between 3 and 30 minutes (e6–e8). Many patients suffer several episodes every day (e7).

Appropriate treatment of BTCP is a great challenge (e9). In all recommendations, drug treatment on

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TABLE 1

Comparative studies of new forms of fentanyl administration

Author, year	n	Comparison	Study design	Main results*	Conflicts of interest
Coluzzi et al. 2001 (6)	93	OTFC versus oral morphine	Double-blind, double-dummy, crossover	Lower PI, higher PID, and greater PR after 15, 30, 45, and 60 minutes with OTFC 33% PI reduction after 15 minutes in 42.3% after OTFC versus 31.8% Better patient evaluations for OTFC	Two coauthors employees of Anesta Corp. (now Cephalon)
Mercadante et al. 2002 (3)	25	OTFC versus IV morphine	Open, randomized	PI after 15 minutes sig. lower in the morphine group (3.3 [2.7 to 3.8] versus 4.1 [3.5 to 4.7]), after 30 minutes no sig. difference	No data
Portenoy et al. 1999 (39)	53	OTFC versus usual medication	Randomized, double-blind	Lower PI, higher PID and greater PR after 15, 30, and 60 minutes with OTFC 56% of the total pain reduction within 15 minutes versus 32%	Two coauthors employees of Anesta Corp. (now Cephalon)
Christie et al. 1998 (40)	46	OTFC versus standard medication	Randomized, double-blind	PID of 0–15 minutes sig. greater (2.35 versus 0.91), sig. lower PI after 15, 30, and 60 minutes and sig. higher overall satisfaction with OTFC	Supported by a grant from Anesta Corp. (now Cephalon), 2 authors employees of and shareholders in Anesta Corp., one a consultant
Ashburn et al. 2011 (15)	180	FBT versus oral oxycodone	Double-blind, double-dummy, crossover	After 15 and 30 minutes higher PID (0.82 ± 1.12 versus 0.6 ± 0.88 ; 1.95 ± 1.47 versus 1.6 ± 1.27) and higher PR (0.69 ± 0.74 versus 0.53 ± 0.67 ; 1.50 ± 0.83 versus 1.23 ± 0.76) with FBT	First author has received funds from ZARS-Pharma, 2 coauthors employees of Cephalon
Mercadante et al. 2009 (22)	86	INFS versus OTFC	Randomized, open, crossover	After 10 and 30 minutes greater PID with INFS (2.27 [1.98 to 2.56] versus 1.08 [0.79 to 1.36] and 4.14 [3.82 to 4.48] versus 3.39 [3.06 to 3.72]), resp. 77.4% of patients preferred INFS More patients found INFS easy/very easy to use (90.1% versus 39.8%)	Study was funded by Nycomed. Six of eight authors have financial connections with relevant pharma companies
Davies et al. 2011 (27)	84	FPNS versus oral morphine	Double-blind, double-dummy, crossover	PID after 15 minutes in the FPNS group sig. higher (3.02 ± 0.21 versus 2.69 ± 0.18), and also after 30, 45, and 60 minutes Sig. higher rate of effective pain reduction (>2 units on an 11-point NRS) after 10 and 15 minutes in the FPNS group (52.4% versus 45.4% and 75.5% versus 69.3%, resp.) Sig. higher rate of complete pain relief (PR = 4) after 15, 30, and 45 minutes (17.6% versus 12.6%, 31.1% versus 21.5%, 50.1% versus 34.3%, resp.)	First author received reimbursement of travel expenses from Archimedes Pharma
Fallon et al. 2011 (28)	110	FPNS versus oral morphine	Randomized, double-blind double-dummy, crossover	Sig. higher PID after 15, 30, 45 and 60 minutes in the FPNS group, no sig. difference after 5 and 10 minutes Sig. higher percentage of episodes showing a reduction in PI by at least 2 points on an 11-point scale after 10 minutes (52.4% versus 45.4%) and 15 minutes (75.5% versus 69.3%), no sig. difference after 5 minutes Sig. higher percentage of episodes with maximal PR (PR = 4) after 30 minutes (17.6% versus 12.6%), 45 minutes (31.1% versus 21.5%) and 60 minutes (50.1% versus 34.3%)	Study was sponsored by Archimedes Development. One coauthor works as a consultant for Archimedes Pharma

For the literature search, the PubMed and Embase databases were searched using the search terms "breakthrough cancer pain" and "fentanyl".

Only randomized, controlled studies were included that compared the effects of fentanyl administered buccally, sublingually, or intranasally with another opioid. Eight publications were found.

*Statistics are given as mean $\pm$ standard deviation or median (95% confidence interval)

OTFC, oral-transmucosal fentanyl citrate; FBT, fentanyl buccal tablets; INFS, intranasal fentanyl spray; FPNS, fentanyl pectin nasal spray;

PI, pain intensity; PID, pain intensity difference; PR, pain relief; IV, intravenous; sig, significant(ly); NRS, numeric rating scale; resp., respectively

TABLE 2

Characteristics of buccal, sublingual, and intranasal fentanyl

Technology	OTFC	FBT	FST	FBSF	INFS	FPNS
Administration route	Lozenge	Buccal tablet	Sublingual tablet	Buccal film tablet	Nasal spray	Nasal spray
Substance	Fentanyl citrate					
Indication	Breakthrough pain in cancer patients on a retarded daily dose of or equivalent to at least 60 mg morphine					
Age restriction	From 16 years	From 18 years	From 18 years	From 18 years	From 18 years	From 18 years
Site of administration	Oral cavity	Buccal, sublingual	Sublingual	Buccal	Nasal	Nasal
Dosage strengths available	6	5	6	5	3	2
	200–400–600–800–1200–1600 µg/tablet	100–200–400–600–800 µg/tablet	100–200–300–400–600–800 µg/tablet	200–400–600–800–1200 µg/tablet	50–100–200 µg/spray	100–400 µg/spray
Absolute bioavailability	50%	65%	70%	71%	89%	Approx. 70% to 90%
Onset of effect	15 min.	15 min.	15 min.	No data	5 to 10 min.	5 min.
Next dose during titration (acc. to SPC)	After 30 min.	After 30 min.	After 15–30 min.	After 30 min.	After 10 min.	After 4 hours
Maximum volume with single dose	1600 µg	800 µg	800 µg	1200 µg	200 µl	800 µg
Smallest package size	3 tablets (= € 43.10)	4 tablets (= € 49.43)	10 tablets (= € 98.16)	Not available at present	10 sprays (= € 106.58)	8 sprays (= € 65.02)
Cheapest price per dose *	11.22 € per tablet	10.11 € per tablet	9.12 € per tablet		€ 9.87 per spray	€ 6.63 per spray

Pharmacological data from summary of product characteristics (SPC) or (Mercadante 2012 [17]). Prices as given by manufacturer.

*Price of a single dose based on data for the smallest available dose in the largest available package acc. to the German Red List.

OTFC, oral transmucosal fentanyl citrate; FBT, fentanyl buccal tablets; FST, fentanyl sublingual tablets; FBSF, fentanyl buccal soluble film tablets; INFS, intranasal fentanyl spray; FPNS, fentanyl pectin nasal spray; acc., according; SPC, summary of product characteristics

demand has a central role, in addition to optimized baseline therapy with extended-release opioids (1–3).

Fentanyl

Fentanyl acts at μ - and, to a lesser degree, also at σ - and κ -opioid-receptors with an analgesic potency that is around 90 times stronger than that of morphine (e10). Being highly lipophilic, it permeates the blood–brain barrier well. Its oral bioavailability is around 25% to 50%.

Fentanyl is mainly metabolized by the liver to the inactive metabolites hydroxyfentanyl and norfentanyl and is excreted renally. About 5% to 10% of the drug is eliminated via the kidneys in an unmetabolized state (e11).

Clinically, the drug is characterized by a rapid onset of action (5–8 minutes to maximum effect after intravenous administration) and short duration of action (30–60 minutes after intravenous administration) (e12).

The fentanyl preparations described below must be strictly differentiated from the transdermal fentanyl preparations available in the past few years that are in-

creasingly being used—sometimes incautious—to treat chronic pain (e13).

Methods

We searched the PubMed (for publications dating from 1946 to May 2012) and Embase databases (for publications dating from 1988 to December 2012), using the search terms “fentanyl” and “breakthrough cancer pain”, for randomized controlled studies in which the use of fentanyl administered by buccal, sublingual, or nasal administration routes in patients with BTCP was compared with another opioid or another fentanyl preparation. The reference lists of systematic reviews and guidelines were searched for further relevant publications. All fentanyl-based drugs licensed for the treatment of BTCP in the German-speaking countries were included.

Screening of titles and abstracts reduced the original 215 hits to 8 relevant publications (Table 1). Six of these compared studies in which various fentanyl preparations were compared with other immediate-release opioids, one compared transmucosal fentanyl with

intravenous morphine, and one compared different fentanyl preparations with each other.

Oral transmucosal fentanyl citrate

With oral transmucosal fentanyl citrate (OTFC), the patient rubs the lozenge on his or her oral mucosa for 15 minutes using an applicator stick. In this way, about one quarter of the fentanyl is absorbed transmucosally; the rest is swallowed with the saliva and enterally absorbed (e14). The swallowed fentanyl undergoes first-pass metabolism in the liver, so that only 52% of the total dose is systemically effective. Maximum plasma concentration is reached after 22 ± 5 minutes; the duration of action is about 2 hours (4, 5).

Several comparative studies and a Cochrane review have shown that OTFC is significantly superior to oral morphine, hydromorphone, and oxycodone in the treatment of BTCP in terms of the extent of pain reduction and time until pain relief is felt (6–8). Compared to oral morphine, a significantly higher rate of episodes with at least 33% pain reduction after 15 minutes was shown (42.3% versus 31.8%). The number needed to treat (NNT) was 9.5 (6).

Compared with intravenous morphine, OTFC showed significantly lower pain reduction after 15 minutes (mean [95% confidence interval]: 4.1 [3.5 to 4.7] versus 3.3 [2.7 to 3.8]). After 30 minutes, the difference was no longer significant. The numbers of episodes in which 33% or 50% pain reduction was achieved were 57% versus 74% and 38% versus 55%, respectively, after 15 minutes, and 85% versus 87% and 75% versus 75%, respectively, after 30 minutes (NNT for intravenously administered morphine: 5.88 and 10, respectively) (9).

OTFC is regarded as well-tolerated in long-term use (10, 11). However, case reports already exist of misuse of the drug (12). A case has been described of dental caries due to the sugary matrix (e15).

In one prospective study, patients given OTFC for BTCP estimated that they saved an average of 1.26 outpatient visits a month (13). One retrospective case series made a similar finding (14). However, because of methodological limitations, however, no conclusions about cost efficiency can be drawn from these studies.

Fentanyl buccal tablets

As a lipophilic substance, fentanyl dissolves poorly in saliva and is poorly absorbed transmucosally. With fentanyl buccal tablets (FBT), locally altering pH allows the ionized form, which is more soluble, to be absorbed more easily, thus increasing transmucosal absorption to 48%. The rest is swallowed and largely metabolized by the first-pass mechanism. The overall bioavailability is 65% (e16). A comparison between FBT and OTFC showed that the time from administration to maximum plasma concentration is significantly shorter for FBT (median: 46.8; range [20.0 to 240.0]) than for OTFC (90.8 [35.0 to 240.1]) (e16).

A clinical comparative study between FBT and rapid-onset oxycodone revealed that after 15 minutes

an average pain reduction of 0.82 ± 1.12 versus 0.60 ± 0.88 visual analog scale (VAS) units was achieved, and after 30 minutes an average of 1.95 ± 1.47 versus 1.60 ± 1.27 . The numbers of episodes with 33% or 50% pain reduction were 13% versus 9% and 6% versus 4%, respectively, after 15 minutes, and 41% versus 32% and 21% versus 16%, respectively, after 30 minutes (NNT between 11 and 50). There was no difference in type and severity of adverse effects (15).

Fentanyl sublingual tablets

With fentanyl sublingual tablets (FST), the first trace of fentanyl in the blood can be demonstrated 8 to 10 minutes after administration; the maximum concentration is seen in a dose-dependent manner after 40 to 58 minutes (16). The bioavailability has not yet been investigated in studies; it is estimated at 70% (17).

We were unable to find a study comparing FST with another opioid for BTCP.

Fentanyl buccal soluble film tablets

Fentanyl buccal soluble film tablets (FBSF) consist of a mucoadhesive layer of active drug that adheres to the mucosa, and a second layer that prevents diffusion into the oral cavity (18). Compared with OTFC, FBSF showed higher peak concentration and drug absorption (19). Bioavailability is 71%. The time to maximum plasma concentration is 90 (45 to 240) minutes (20).

Although FBSF was licensed for the European market in April 2011, it is not yet freely available. There are no clinical studies comparing FBSF with other opioids in treatment for BTCP.

Intranasal fentanyl spray

Intranasal administration (intranasal fentanyl spray, INFS) is increasingly being used as an alternative way to give drugs. It is familiar to the patient (or is easy to learn), can be carried out without assistance, is reliable, and allows rapid uptake of the drug (21). By avoiding the oral route, nasal administration is a good option in, for example, patients with impaired gastrointestinal function, nausea or vomiting, oral mucositis, or xerostomy (22), and makes it easier to care for patients with dysphagia.

The nasal bioavailability of INFS is 70% to 90% (23). Maximum plasma concentration is reached after 9 to 15 minutes (24).

One study compared the clinical efficacy of INFS versus OTFC to treat BTCP. At the end of 10 minutes after administration of INFS, pain had reduced by an average of 2.27 (95% confidence interval [CI]: 1.89 to 2.56) VAS units, versus 1.08 (0.79 to 1.36) for OTFC, and at the end of 30 minutes it had reduced by 4.15 (3.82 to 4.48) versus 3.39 (3.06 to 4.48) for OTFC. A significant difference was shown for pain reduction between 5 and 60 minutes. The proportions of episodes in which pain was reduced by 33% or 50% after 5 minutes were 25.3% versus 6.8% and 12.8% versus 2.1%, respectively. After 10 minutes they were 51.0% versus 23.6% and 36.9% versus 9.7%, respectively (NNT 5.4

and 9.4, and 3.7 and 3.7, respectively). The authors conclude that INFS has distinct advantages over other treatments for BTCP (22). Adverse effects occurred with INFS in 45.9% of cases, and in 34.7% with OTFC. In both groups, the most common adverse effects were nausea, vomiting, and constipation.

A meta-analysis showed that, when given for BTCP, INFS brings greater pain reduction in the first 15 minutes than FBT, OTFC, or oral morphine (24).

Fentanyl pectin nasal spray

The most recent development is a combination of INFS with pectin (fentanyl pectin nasal spray, FPNS). Pectin improves absorption by forming a gel layer from which fentanyl penetrates the mucosa (25). This alters the pharmacological profile, reducing the initial peak concentration while keeping the same rapid onset of action, with the aim of reducing adverse effects (26).

In a comparative study with oral immediate-release morphine, FPNS showed better efficacy at the start of a pain episode. Pain reduction by two VAS units was achieved in, respectively, 52.4% versus 45.4% of patients after 10 minutes, and 75.5% versus 69.3% after 15 minutes (NNT: 14.3 and 16.1, respectively) (27). In another study, the average pain reduction at 15 minutes was 3.02 ± 0.21 VAS units (mean $\pm$ standard error) after FPNS versus 2.69 ± 0.18 after oral morphine. The significant difference continued to exist up until minute 60 (28).

In a long-term observational study, 96.9% of patients were satisfied with FPNS. Mild to moderate opioid-specific adverse effects were reported by 24.6% of patients. According to Radbruch et al., even when given long-term, FPNS is a safe and well-tolerated drug (29).

Discussion

In recent years, several rapid-onset fentanyl preparations have been licensed for the treatment of BTCP. Of the eight clinical studies identified in the literature search, six compared buccal, sublingual, or intranasal forms of fentanyl with oral immediate-release opioids. In all these studies, a significantly lower pain intensity or a higher percentage of episodes with 33% or 50% pain reduction was shown with fentanyl, especially at earlier pain measurement times (Table 1). These findings are also reflected in systematic reviews (8, 30). In one comparative study between OTFC and intravenous morphine, OTFC was clinically inferior because it had a slower onset of action.

Only a single randomized controlled study compared different forms of administration of fentanyl with each other. This study showed that, compared to OTFC, INFS gave significantly greater pain reduction after only 5 minutes, and doubled the number of episodes with 33% pain reduction at 10 minutes and 30 minutes (22). Pharmacological and meta-analytical data showed that the clinical significance of this advantage remained when OTFC was compared to other rapid-onset forms of fentanyl (24).

A meta-analysis of six comparative studies came to the conclusion that, within the first hour, at all measuring time points, FBT, OTFC, and INFS achieved significantly greater pain reduction than placebo, whereas oral immediate-release morphine showed a superior effect to placebo only after 45 minutes. The study reported that at 15 and 30 minutes, INFS achieved significantly greater pain reduction than FBT, OTFC, or oral morphine (24). From a scientific point of view, however, there is an urgent need for further comparative studies.

Tolerability—including over the long term—is represented as good (10, 11, 29). Nevertheless, it must be emphasized that fentanyl is a highly potent opioid, the use of which—especially in galenic forms—leads to peak concentrations similar to those of intravenous administration, and thus needs to be handled responsibly by both doctors and patients. There are already case reports on its misuse by patients being treated palliatively (12). A retrospective company-sponsored study quantified the risk of aberrant behavior in relation to FBT use in patients with BTCP as 11% (31). Accordingly, great care should be taken over deciding when to employ this drug, and over patient information and monitoring (30, 32).

Early attempts to use these drugs to relieve pain from nonmalignant causes (33, 34) must also be viewed with reservation. A systematic review of breakthrough non-cancer pain concludes that there is no evidence base for the use of immediate-release opioids in this setting (35). In addition, it must be emphasized that the new fentanyl preparations are licensed exclusively for use in BTCP in patients already receiving a retarded daily dose equivalent of at least 60 mg morphine.

An important point is the matter of cost. Although fentanyl itself is very cheap, the new galenic preparations are considerably more expensive than existing alternatives. Immediate-release hydromorphone, oxycodone, and morphine cost about € 0.95 to € 1.82 per single dose, while the prices of rapid-onset fentanyl preparations are € 6.63 to € 11.22 per single dose (Table 2). A few studies have attempted to compare these figures with the greater cost savings achieved in reduced hospital or doctor visits (13, 14, 36), but they are methodologically inadequate to allow such far-reaching conclusions to be drawn.

Vissers et al. attempted to quantify the economic effects of treating BTCP with fentanyl preparations in patients with a life expectancy of 180 days. Building on six original articles and adjusting for the Swedish public health system, they developed a model for comparing resource use with quality-adjusted years of life (QALYs). INFS gave rise to the highest costs (€ 5534; OTFC: € 5708; FBT: € 5011; placebo € 877), but also achieved the highest QALY values (0.266; OTFC: 0.220; FBT: 0.223; placebo 0.167) (36). It should be added that this analysis was funded by Nycomed.

For clinical purposes, an important finding is that, unlike with traditionally used drugs, for the fentanyl preparations described, no correlation was found

between extended-release daily dose and the dosage of the rapid-onset on-demand medication (37). Individually tailored, gradually increasing dose titration is recommended. Since this titration process reduces compliance, the possibility has been contemplated of skipping over the lowest dosages in high-dose opioid therapy (38). When switching between different fentanyl preparations, the differences in bioavailability must be taken into account (Table 2).

Limitations

The main limitation of this review is that it is based on only eight comparative studies, most of them closely connected to the pharmaceutical industry, that show great heterogeneity in terms of both study populations and studied variables (Table 1). For this reason, many important questions remain unanswered, e.g., the practical relevance of the differences described, the economic aspects, and the potential for dependency/misuse. Further, independent studies are therefore urgently needed.

Summary

Thanks to their pharmacological profile, the new fentanyl preparations extend the possibilities for treating BTCP. Because they lead to a higher rate of significant pain reduction within a short time than do conventional immediate-release oral opioids, their use appears to be advantageous, especially in patients with strong rapid-onset, short-lasting BTCP.

KEY MESSAGES

- New galenic preparations of fentanyl offer a fast, noninvasive, easily administered alternative in the treatment of breakthrough cancer pain (BTCP). At the present time, various buccal, sublingual, and nasal systems are available.
- Six studies compared various fentanyl preparations with immediate-release oral opioids in the treatment of BTCP. All these studies showed fentanyl to be associated with significantly lower pain intensity or a higher percentage of pain episodes in which pain was reduced by 33% or 50%, especially at early measuring time points.
- In one comparative study, oral transmucosal fentanyl citrate (OTFC) was clinically inferior to intravenous morphine because of its slower onset of action.
- A direct comparison of intranasal fentanyl spray (INFS) with OTFC showed significantly strong pain reduction at all measuring time points between 5 and 60 minutes for INFS. The percentages of episodes with 33% and 50% pain reduction after 10 minutes were respectively doubled and trebled by intranasal administration.
- Titration should start with the smallest dose and only then be increased.
- When switching between forms of fentanyl administration, different effective doses must be expected because of the differing bioequivalencies.

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Conflict of interest statement

Professor Sandner-Kiesling has had conference attendance fees and travel expenses reimbursed by Pfizer, Mundipharma, Cephalon, Grünenthal, and Fresenius. He has received lecture fees from Cephalon and Grünenthal.

The other authors declare that no conflict of interest exists.

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REVIEW ARTICLE

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