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Time-dependent Efficacy of Bacterial Filters and Infection Risk in Long-term Epidural Catheterization

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Background: **Epidural infection represents a serious albeit infrequent complication of long-term epidural catheterization. The catheter hub is regarded as the main point of entry for microorganisms among the three possible routes (hematogenous, insertion site, hub) of microbial colonization of the inserted catheter. The current study was aimed at evaluating whether frequent changing of antimicrobial filters carries an increased risk of catheter hub contamination and the time-dependent efficacy of commonly used antimicrobial filters after prolonged use.**

Methods: **In the first part of the study, a microbiologic survey (skin, filter, hub, and catheter tip) was performed weekly in a group of 47 patients with cancer bearing subcutaneously tunneled catheters managed at home. Subsequently, the time-dependent efficacy of 96 micropore filters (32 Portex, 32 Sterifix-Braun, 32 Encapsulon TFX-Medical) differing in surface areas and/or composition of the filtering membrane was evaluated in a laboratory study. Filters were perfused, under the usual conditions of clinical use (flow resistance, injection pressure, temperature), every 8 h up to 60 days, with 5 ml of two different analgesic solutions, either sterile or containing 1.5×10^5/ml of *Streptococcus milleri I.* Eight filters of each type subsequently were flushed with a *S. milleri* suspension (0.5 McFarland) after 7, 14, 28, and 60 days of continuous perfusion, and the resulting filtrates were cultured.**

Results: **In 16 of 19 positive hub cultures, the same microorganisms (species, biotype, antibiotype) were cultured from skin and filters. A statistically significant positive trend was found between the number of filter changes and the rate of positive hub cultures (χ_1^2 trend 5.11; $P = 0.02$). A high correlation coefficient was found between number of positive skin cultures and number of positive filtrates ($r = 0.88$; $P = 0.01$) and between number of positive filtrates and number of positive hub cultures ($r = 0.93$; $P = 0.003$). Cultures obtained from Portex and Sterifix-Braun filters yielded no bacterial growth (64/64) throughout the study period. Cultures from Encapsulon TFX-Medical filters showed bacterial growth 2/8 at seventh day, 7/8 at the 14th day, and 16/16 from the 28th day onward.**

Conclusions: **Our data indicate significant correlation between the incidence of catheter hub colonization and the filter-change frequency, when the skin close to the filter-hub connection is contaminated. Our results also show that Portex and Sterifix-Braun bacterial filters, when perfused with reduced volumes at low injection pressures, maintain an unmodified antimicrobial function for at least 60 days. Based on these data, it appears clinically feasible to reduce the frequency of filter changes during long-term epidural catheterization, with a consequent possible decrease of epidural catheter colonization. (Key words: Complications: catheter-related infection. Equipment: antimicrobial filters. Techniques: epidural.)**

DURING the past 10 yr, long-term epidural opioid infusion has been used to provide analgesia for cancer pain management.[1–4] Among possible complications of such a procedure, the microbial colonization of epidural space remains the most serious because of the delayed appearance of related symptoms. In addition, compression of the spinal cord and/or alterations of local vascularization, due to possible abscess development, may lead to neurologic complications that are sometimes irreversible.[5–8]

In large retrospective studies, epidural infection associated with long-term epidural anesthesia and/or analgesia has been regarded as a rare occurrence.[5,6,9] However, prospective clinical studies have revealed a prevalence of positive bacterial cultures as great as 22% from routine testing of epidural catheters.[10,11] In a study by Hunt *et al.*[11] on the possible routes of catheter microbial colonization, the insertion site and the catheter hub accounted for 32% and 40%, respectively. More recently, Du Pen *et al.*[12] conducted a prospective study on 350 patients with subcutaneously tunnelled epidural catheters for treatment of cancer or AIDS-related pain. By radiography, magnetic resonance imaging, and

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microbial cultures, epidural infections were detected in 5.4% of the patients.[12] The routes by which microorganisms colonized the epidural space were hematogenous in 20% of the cases, the catheter tunnel (starting at the insertion site of the catheter) in 26%, and the catheter hub in 54% of the patients. These results are comparable to those from other studies concerning microbial colonization routes of central venous catheters.[13,14]

Because the catheter hub appears to represent the main route of catheter microbial colonization, as suggested by the above-mentioned data, the use of bacterial filters should represent a valuable tool for preventing epidural colonization related to such a route. However, some authors have reported cases of epidural infections *via* the hub despite the use of filters.[12] There are two possible explanations for such observations: (1) the filter loses its antimicrobial efficacy after a prolonged use, and (2) the catheter hub is directly contaminated during filter-changing maneuvers, thereby bypassing the filter barrier. If the catheter hub is directly contaminated during the filter-changing maneuvers and filters preserve their antimicrobial activity over a prolonged use, a reduction in filter-change frequency may result in a lower risk of epidural infection during long-term catheterization.

To test such hypotheses, we evaluated the actual risk of hub contamination as a function of filter-change rates in a clinical setting and the time-dependent efficacy of commonly available bacterial filters under controlled laboratory conditions. For the latter study, three commercially available bacterial filters differing in surface area and/or material of the filtering membrane were tested during long-term perfusion with commonly used analgesic solutions.

Methods and Materials

Clinical Study

Over a period of 8 months, 47 patients with advanced cancer in whom subcutaneously tunneled epidural catheters (Portex) had been placed were studied. During each of seven weekly subsequent out-patient visits, along with filter change, we performed (1) a skin swab at catheter insertion site and around the sutures fixing the catheter hub (4 cm^2 of skin area comprising the Luer-Lok connection of the filter), (2) a culture of the filtrate (removed filters were flushed with 5 ml 0.5 McFarland suspension of *Streptococcus milleri I*), (3) a swab of the catheter hub inside surface, and (4) a culture of the tip at catheter withdrawal.

Catheters were removed when hub culture results were positive, if signs of catheter tunnel or epidural space infection were present, in the presence of catheter mechanical dysfunction or when the analgesic procedure was clinically ineffective. Details of clinical procedures and microbiologic investigations were described previously.[14] The significance of statistical differences between proportions was tested by means of χ_1^2 test for trend and by means of correlation coefficient for continuous variables.[15] A significant difference was accepted when $P < 0.05$.

Laboratory Study

Ninety-six micropore "flat" bacterial filters with a membrane pore size of 0.2 μm were studied: 32 Portex (Portex LTD, Hythe, Kent, England), 32 Sterifix-Braun (B. Braun, Melsungen, Germany), and 32 Encapsulon-TFX Medical (Corning Costar, Cambridge, MA). Surface area of the filtering membranes was 4.91 cm^2 for Portex, 4.7 cm^2 for Sterifix-Braun, and 3.2 cm^2 for Encapsulon-TFX Medical filters. Composition of the filtering membrane was nylon for Portex and Sterifix-Braun, and cellulose acetate for Encapsulon-TFX Medical filters.

To exclude biases related to manufacturing defects, four filters of each type were randomly taken from filter packages in current use at our institution and subjected to a functional test. Filters were perfused with *S. milleri I* bacterial suspension of a known titer, and the resulting filtrates underwent culture in aerobic Bactec vials type NR6A (Becton Dickinson, Sparks, MD). After a negative result for all the cultures, the study was started.

To reproduce the usual conditions of flow resistance, injection pressure, and temperature, each filter was connected, under strict aseptic conditions, to a Portex epidural catheter of 0.9 mm in external diameter, which was, in turn, inserted in an empty sterile polyvinylchloride bag; 20-ml syringes were used for injection, and all filters were kept at 36°C (the usual temperature at the skin-filter interface during clinical use).

To test filter efficacy against the usual chemical and physical conditions, we used sterile analgesic solutions. Filters also were tested with contaminated analgesic solutions to account for a possible increase of bacterial burden over time.

In two consecutive phases of the study, filters were perfused, by the same trained nurses, with two different analgesic solutions of routine use at our institution: (1) SDM solution, consisting of 18 ml of normal saline,

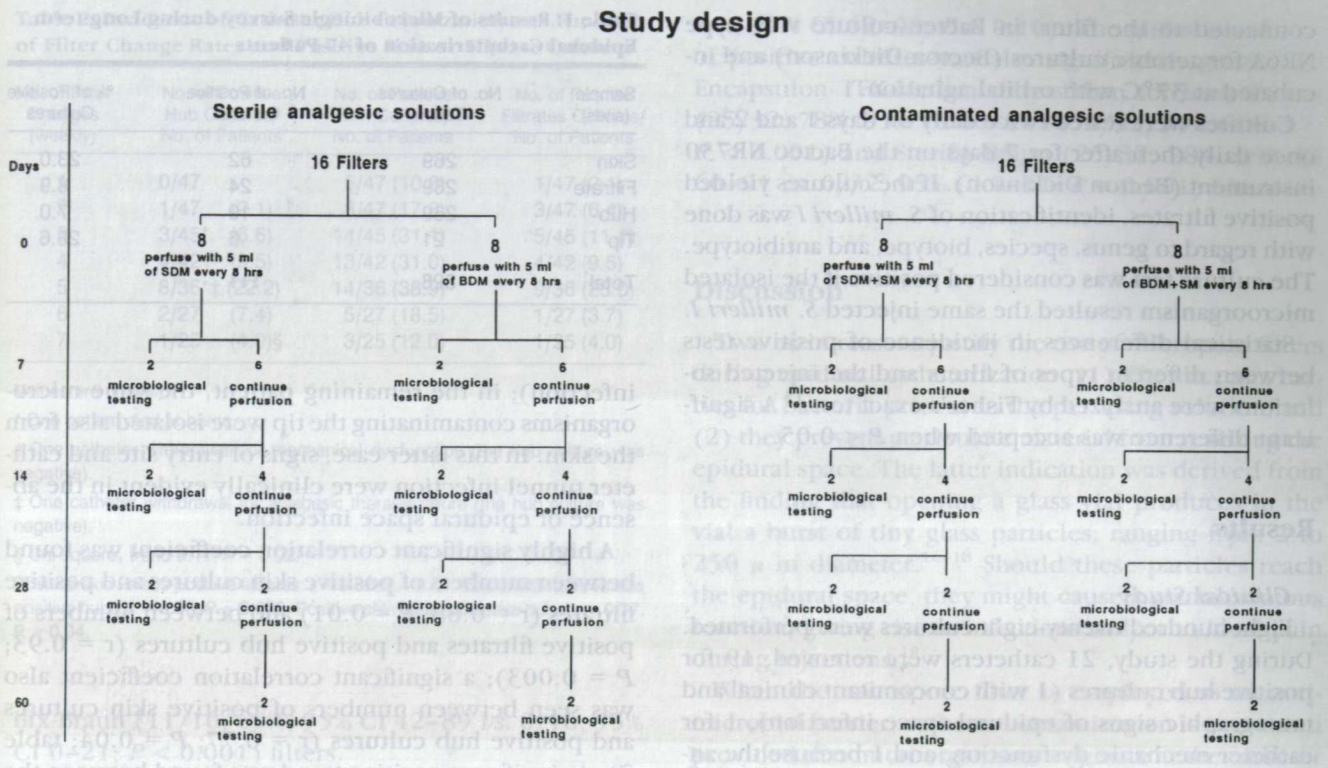

Fig. 1. Study design. The described procedure was adopted for 32 bacterial filters from each of the following manufactures: Portex LTD (Hythe, Kent, England), B. Braun (Melsungen, Germany), and Corning Costar (Cambridge, MA). At the indicated times, filtrates were subjected to microbial cultures as indicated in methods. SDM = normal saline, dexamethasone, and morphine hydrochloride; BDM = bupivacaine, dexamethasone, and morphine hydrochloride; SM = *Streptococcus milleri I* at a final titer of 1.5×10^5 bacteria/ml.

1 ml (4 mg) Dexamethasone, and 1 ml (10 mg) morphine hydrochloride, and (2) BDM solution, consisting of 18 ml 0.25% bupivacaine, 1 ml (4 mg) Dexamethasone, and 1 ml (10 mg) morphine hydrochloride. In the first phase, 48 filters were perfused with sterile analgesic solutions. In the second phase, 48 other filters were conversely perfused with analgesic solutions contaminated by *S. milleri I* (SM) at a final titer of 1.5×10^5 bacteria/ml.

The *p*H and osmolality of the solutions were, respectively, 6.91 and 268 for SDM, 6.65 and 251 for BDM, 6.83 and 276 for SDM + SM, and 6.53 and 255 for BDM + SM.

Of 32 filters of each type, 8 were perfused every 8 h with 5 ml of SDM, 8 with 5 ml of BDM, 8 with 5 ml of SDM + SM, and 8 with 5 ml of BDM + SM. After 7, 14, 28, and 60 days of perfusion, eight filters of each type (two perfused with SDM, two with BDM, two with SDM + SM, and two with BDM + SM) were detached from the catheters and subjected to functional testing at the microbiology laboratory (fig. 1). Tests were performed by a bacteriologist "blinded" as to the type of both the flushed solution and filter.

Microbiologic Investigations. The organism used in this study was a clinical strain of recently isolated Streptococcus (*S. milleri I,* diameter 1–1.5 μm) grown in blood agar. From the colonies of this microorganism, a suspension of 0.5 McFarland (corresponding to 1.5×10^8 bacteria/ml) was prepared in tryptic soy broth drawn from Bactec culture vials, type NR6A (enriched soybean—casein digest broth with carbon dioxide), for aerobic cultures (Becton Dickinson).

Filters were flushed with 5 ml of this suspension, and the resulting filtrates were directly injected, by a needle

connected to the filter, in Bactec culture vials type NR6A for aerobic cultures (Becton Dickinson) and incubated at 37°C with orbital agitation.

Cultures were tested twice daily on days 1 and 2 and once daily thereafter for 7 days on the Bactec NR730 instrument (Becton Dickinson). If the cultures yielded positive filtrates, identification of *S. milleri I* was done with regard to genus, species, biotype, and antibiotype. The culture test was considered positive if the isolated microorganism resulted the same injected *S. milleri I.*

Statistical differences in incidence of positive tests between different types of filters and the injected solutions were analyzed by Fisher's exact test.[15] A significant difference was accepted when $P < 0.05$.

Results

Clinical Study

Eight hundred twenty-eight cultures were performed. During the study, 21 catheters were removed, 19 for positive hub cultures (1 with concomitant clinical and tomographic signs of epidural space infection), 1 for catheter mechanic dysfunction, and 1 because the analgesic procedure turned to be clinically ineffective. In 24 patients who continued the therapy and in 2 who deceased at home, the catheter tip was not available for evaluation. All microbiologic results are reported in table 1.

Eighty-nine of 111 positive cultures showed growth of gram-positive organisms, and in the remaining 22, gram-negative rods were cultured.

Skin cultures were positive once in six patients, twice in six patients, three times in eight patients, and four times in five patients. In 22 patients, skin cultures were always negative.

Although the injected *S. milleri I* was never cultured, 24 filtrates yielded bacterial growth. In 16 of 24 positive filtrates, isolated microorganisms were the same (species, biotype, antibiotype) colonizing both the hub and the skin; in 6 other cases, the same microorganisms were isolated from the skin alone; and the source was not identified in the remaining 2.

Positive cultures from 19 hubs showed the same isolates from filtrates in 16 cases and from skin in 18 instances. In one case, microorganisms were cultured from the hub alone.

In five of six (83%) positive tip cultures, isolates were the same obtained from the catheter hub (one patient had clinical and tomographic signs of epidural space infection); in the remaining patient, the same microorganisms contaminating the tip were isolated also from the skin. In this latter case, signs of entry site and catheter tunnel infection were clinically evident in the absence of epidural space infection.

Table 1. Results of Microbiologic Survey during Long-term Epidural Catheterization of 47 Patients

Sample (sites)	No. of Cultures Taken	No. of Positive Cultures	% of Positive Cultures
Skin	269	62	23.0
Filtrate	269	24	8.9
Hub	269	19	7.0
Tip	21	6	28.6
Total	828	111	

A highly significant correlation coefficient was found between numbers of positive skin cultures and positive filtrates ($r = 0.88$; $P = 0.01$) and between numbers of positive filtrates and positive hub cultures ($r = 0.93$; $P = 0.003$); a significant correlation coefficient also was seen between numbers of positive skin cultures and positive hub cultures ($r = 0.77$; $P = 0.04$; table 2). A significant positive trend was found between the number of filter changes and the rate of positive hub cultures (χ_1^2 trend 5.11; $P = 0.02$; table 2).

Laboratory Study

Use of Sterile Solutions. After 7 days of perfusion, filtrates of all the tested filters (four of each type) perfused with two analgesic solutions (two with SDM and two with BDM) yielded negative cultures. At day 14, two Encapsulon TFX-Medical filters perfused with SDM solution and one Encapsulon TFX-Medical filter perfused with BDM solution yielded positive filtrates. Filtrates from all Portex and Sterifix-Braun filters were negative at 28 and 60 days, whereas all cultures from Encapsulon-TFX Medical filtrates yielded bacterial growth.

Growth of microorganisms different from *S. milleri I* was never observed.

There were no significant differences between Encapsulon TFX-Medical filters perfused with SDM solution (6/8, 75% positive test, 95% CI 35–97) and those perfused with BDM solution (5/8, 63% positive test, 95% CI 25–92; $P = 0.36$). The incidence of positive cultures was significantly greater for Encapsulon TFX-Medical filters than for both Portex (11/16, 69%, 95% CI 42–89 *vs.* 0/16, 95% CI 0–21; $P < 0.001$) or Ster-

Table 2. Incidence of Catheter Hub Colonization as a Function of Filter Change Rates and Positive Skin or Filtrate Cultures

No. of Filter Changes (weekly)	No. of Positive Hub Cultures/ No. of Patients	No. of Positive Skin Cultures/ No. of Patients	No. of Positive Filtrates Cultures/ No. of Patients
1	0/47	5/47 (10.6)	1/47 (2.1)
2	1/47 (2.1)	8/47 (17.0)	3/47 (6.4)
3	3/45* (6.6)	14/45 (31.1)	5/45 (11.1)
4	4/42† (9.5)	13/42 (31.0)	4/42 (9.5)
5	8/36*‡ (22.2)	14/36 (38.9)	9/36 (25.0)
6	2/27 (7.4)	5/27 (18.5)	1/27 (3.7)
7	1/25 (4.0)§	3/25 (12.0)	1/25 (4.0)

Values are no. (%).

* One patient died at home.

† One catheter withdrawal for mechanical dysfunction (the hub culture was negative).

‡ One catheter withdrawal for analgesic therapy failure (the hub culture was negative).

§ Chi-square, trend 5.11; $P = 0.02$.

Positive skin *versus* positive filtrates: $r = 0.88$, $P = 0.01$. Positive filtrates *versus* positive hubs: $r = 0.93$, $P = 0.003$. Positive skin *versus* positive hubs: $r = 0.77$, $P = 0.04$.

ifix-Braun (11/16, 69%, 95% CI 42–89 *vs.* 0/16, 95% CI 0–21; $P < 0.001$) filters.

Use of Contaminated Solutions. After 7 days of perfusion, two Encapsulon TFX-Medical filters (one perfused with SDM + SM solution and one perfused with BDM + SM solution) yielded positive filtrates. All cultures from Encapsulon TFX-Medical filtrates yielded bacterial growth at days 14, 28, and 60. All cultures obtained from Portex and Sterifix-Braun filtrates resulted in no bacterial growth (64/64) throughout the study period.

Growth of microorganism different from *S. milleri I* was never observed.

There were no differences between Encapsulon TFX-Medical filters perfused with SDM + SM solution (7/8, 88% positive test, 95% CI 47–100) and those perfused with BDM + SM solution (7/8, 88% positive test, 95% CI 47–100; $P = 0.50$). The incidence of positive cultures was significantly greater for Encapsulon TFX-Medical filters than for both Portex (14/16, 88%, 95% CI 62–98 *vs.* 0/16, 95% CI 0–21; $P < 0.001$) and Sterifix-Braun (14/16, 88%, 95% CI 62–98 *vs.* 0/16, 95% CI 0–21; $P < 0.001$) filters.

Overall, no differences were observed between Encapsulon TFX-Medical filters perfused with sterile solutions, SDM and BDM (11/16, 69% positive test, 95% CI 41–89), and those perfused with contaminated solutions, SDM + SM and BDM + SM (14/16, 88% positive test, 95% CI 62–98; $P = 0.16$). The global incidence of positive cultures was also significantly greater for Encapsulon TFX-Medical filters than for both Portex (25/32, 78%, 95% CI 60–91 *vs.* 0/32, 95% CI 0–11; $P < 0.001$) and Sterifix-Braun (25/32, 78%, 95% CI 60–91 *vs.* 0/32, 95% CI 0–11; $P < 0.001$) filters.

Discussion

Two main reasons justify the use of micropore filters during epidural catheterization: (1) They act as a barrier for bacteria present in the perfusing solution, and (2) they prevent particulate material from reaching the epidural space. The latter indication was derived from the finding that opening a glass vial produces in the vial a burst of tiny glass particles, ranging from 2 to 250 μ in diameter.[16–18] Should these particles reach the epidural space, they might cause a granulomatous reaction, giving rise to infections and/or to local pain during injections.[18]

When the micropore filter is employed as an antimicrobial barrier, catheter contamination is prevented provided that microorganisms originate at the catheter hub. In fact, at least three possible routes cause microbial colonization of catheter and/or of epidural space: hematogenous, from distant sources[7,12,19]; the catheter insertion site[11,12]; and the catheter hub.[11,12,20]

In cases wherein microbial colonization of the catheter and/or epidural space were observed, some authors indicated the catheter hub as the main point of entry for microorganisms.[11,12] This evidence appears somewhat surprising because all of the catheters studied were supplied with bacterial filters. On the other hand, many studies on central venous catheters have demonstrated that the main route of microbial colonization is the catheter hub,[14,21] which appears to be contaminated during tubing changes.[14,22,23]

Based on the above considerations, the first part of our study was aimed at evaluating the actual risk of hub colonization as a function of filter-change rates in a clinical setting. If the catheter was directly contaminated during the filter-change maneuvers and the filters preserved their antimicrobial activity over a prolonged use, a reduction in filter-change frequency might result in a lower risk of catheter colonization during long-term catheterization. The second part of this study therefore was aimed to test the time-dependent efficacy of filters during long-term infusion with commonly used analgesic solutions.

Our results showed a high rate of positive skin cultures (23%) despite special training in use of aseptic techniques for nurses who changed dressings. This may be related to occasional dislodgement (between changes) of the occlusive dressing in patients less careful in catheter management at home.

The high correlation coefficients between number of positive skin and filtrates cultures (isolates were the same in 16 of 24 instances) and between the number of positive filtrates and hub cultures (isolates were the same in 16 of 19 instances) suggest that the Luer-Lok connection of the filter, contaminated by the skin flora, might trail microorganisms from the skin to the hub during filter change. Furthermore, this hypothesis is supported by the significant positive trend found between the number of filter changes and the rate of positive hub cultures (χ_1^2 trend 5.11; $P = 0.02$). From our results, filter change is to be considered as a maneuver at major risk of causing hub colonization when the skin close to the filter hub connection is contaminated. According to results of other authors,[11-12] catheter hub resulted the main route of microbial colonization of the epidural catheter (83% positive tip cultures had the same isolates of the hub cultures).

From our laboratory study, we have shown that Portex and Sterifix-Braun bacterial filters maintain an intact antimicrobial function for at last 60 days of continuous use, also when the injected solution is highly contaminated. Encapsulon TFX-Medical filters showed an unmodified function only for 7 days, when sterile solution was injected, whereas they did not maintain such antimicrobial function when a high titer of microorganisms was present in the injected solutions.

Overall, the diminished efficacy after prolonged use of Encapsulon TFX-Medical compared to that of Portex and Sterifix-Braun filters, probably can be ascribed to the different material of the filtering membrane; *i.e.* nylon for Portex and Sterifix-Braun filters and cellulose acetate for Encapsulon TFX-Medical filters.

Our results show that Portex and Sterifix-Braun bacterial filters, when perfused at a low injection pressure (20 ml syringes) with reduced volumes (5 ml, 3 times daily) of the usually employed analgesic solutions, maintain an unmodified function also against an increased bacteriologic burden over a period of at least 60 days. This period is much longer than that usually suggested by manufacturers (hours or a few days).

Based on these data, it appears feasible to reduce the frequency of filter change during long-term epidural catheterization, with a likely reduction of epidural infection risk, deriving from bacterial colonization of the catheter hub. This strategy, however, should not promote negligence in sterile manipulations during preparation and injection of the analgesic solution nor diminish the aseptic measures during dressing and filter changes. The prolonged use of bacterial filters during home care procedures provides psychological benefit to the patient by reducing the need for frequent outpatient visits.

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